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(54) Title: TOLL-LIKE RECEPTOR 9 (TLR9) FROM VARIOUS MAMMALIAN SPECIES
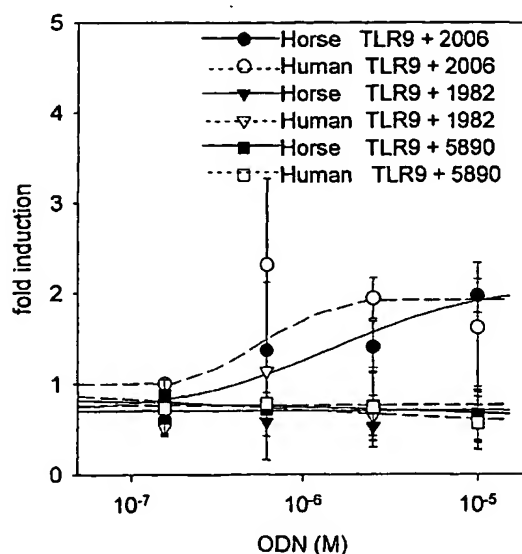
(57) Abstract: Novel amino acid and nucleotide sequences for rat, pig (porcine), cow (bovine), horse (equine), and sheep (ovine) Toll-like receptor 9 (TLR9) are provided. Also provided are amino acid and nucleotide sequences for dog (canine), cat (feline), mouse (murine), and human TLR9. Comparison of these sequences, especially in combination with functional assessment for species-specific CpG motif preferences, permits identification of specific regions and amino acid residues of interest in TLR9 ligand interaction. Novel chimeric TLR9 receptor molecules, cells expressing these molecules, and methods for their use in screening assays for TLR9 ligands are also provided.

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TOLL-LIKE RECEPTOR 9 (TLR9) FROM VARIOUS MAMMALIAN SPECIES

Background of the Invention

Synthetic oligodeoxynucleotides (ODN) and DNA containing immunostimulatory CpG motifs (CpG DNA) function as potent adjuvants and activators of the innate immune system. Heeg K et al. (2000) *Int Arch Allergy Immunol* 121:87-97; Krieg AM (2001) *Vaccine* 19:618-22. A wide variety of CpG-containing sequences have been screened for biological activity and it is reported that optimal CpG DNA sequences can vary among species. Rankin R et al. (2001) *Antisense Nucleic Acid Drug Dev* 11:333-40.

Toll-like receptor 9 (TLR9) has recently been identified as a receptor for CpG ODN. Hemmi H et al. (2000) *Nature* 408:740-5. The molecular mechanism by which TLR9 recognizes CpG DNA is not understood.

Summary of the Invention

Toll-like receptor 9 (TLR9) is known to be involved in innate immunity and to signal in response to CpG DNA. To date, the amino acid sequences only of human and murine TLR9 have been reported, and, interestingly, these two species are known to prefer different CpG motifs. The structural basis for this species-specific CpG motif preference has not yet been fully elucidated. The instant invention provides, in part, novel amino acid and nucleotide sequences of rat, pig, cow, and horse TLR9. These novel TLR9 sequences are useful for elucidating certain key structural features of TLR9. Specifically, comparison of sequences of murine, human, and these novel TLR9 sequences permits identification of areas of highly conserved sequence, areas of group conservation, and areas of hypervariability. In addition, such comparisons permit an assessment of evolutionary relatedness among TLR9 molecules of the various species, as well as an assessment of inter-species homologies. Importantly, such comparisons permit a rational basis for identifying amino acids in TLR9 that may be involved in the CpG binding site, as well as amino acids involved in conferring species specificity for particular CpG motifs. Such information may be used to design and construct novel TLR9 molecules which incorporate specific point or regional mutations and which possess desired ligand binding characteristics. Such information may also be useful in designing and identifying novel ligands for TLR9 of a given species.

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In one aspect, the invention provides isolated polypeptides having amino acid sequences for rat, pig (porcine), cow (bovine), horse (equine), and sheep (ovine) TLR9 polypeptides. These amino acid sequences correspond to SEQ ID NOs 1, 5, 9, 13, and 17, respectively. Each of these sequences is believed to include at least a majority of an extracellular domain, as well as a transmembrane region and at least part of a TLR/IL-1 receptor (TIR) domain. To the extent any such sequence may lack an amino-terminal and/or carboxy-terminal sequence, such sequence is ascertainable, without undue experimentation, using conventional molecular biology techniques and the sequence information provided herein.

In another aspect the invention provides isolated polypeptides having amino acid sequences for essentially the whole extracellular domain, optionally including a signal peptide, of each of rat, porcine, bovine, equine, and ovine TLR9. These amino acid sequences correspond to SEQ ID NOs 2, 6, 10, 14, and 18, respectively. Such extracellular domains are believed to include sequence specifically involved in binding to TLR9 ligand, such as CpG DNA. In addition, such extracellular domains are believed to include sequence that confers species specificity for particular CpG motifs.

Isolated nucleic acid molecules encoding the polypeptides just described above are also provided according to further aspects of the invention. Such nucleic acid molecules include, but are not limited to, nucleic acid molecules having sequences provided by SEQ ID NOs 3, 7, 11, 15, 19; and 4, 8, 12, 16, and 20, respectively. Isolated nucleic acid molecules encoding the TLR9 polypeptides of SEQ ID NOs 1, 5, 9, 13, 17; and 2, 6, 10, 14, and 18 also include nucleic acid molecules that differ in sequence from SEQ ID NOs 3, 7, 11, 15, 19; and 4, 8, 12, 16, and 20, respectively, due to degeneracy of the genetic code. Such nucleic acid molecules will hybridize, under stringent conditions, with suitably selected nucleic acid molecules having sequences selected from SEQ ID NOs 3, 4, 7, 8, 11, 12, 15, 16, 19, and 20.

In another aspect the invention provides a vector which includes an isolated nucleic acid molecule of the invention. In one embodiment the vector is an expression vector and the isolated nucleic acid molecule of the invention is operably linked to a regulatory sequence in the vector. When present within a cell, an expression vector according to this aspect of the invention causes the cell to express a polypeptide of the invention.

The invention according to another aspect provides a cell in which a vector of the invention is present. In one embodiment the cell containing the vector expresses a

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polypeptide of the invention. In certain embodiments the cell also contains a reporter construct that transduces a TLR9-mediated signal in response to contact of the polypeptide of the invention or a TLR9 with a suitable TLR9 ligand. The cell containing the vector, and optionally containing the reporter construct, can be used in screening methods also provided

5   by the invention.

In yet another aspect the invention provides an antibody or antibody fragment that binds specifically to an isolated polypeptide of the invention. In certain embodiments the antibody or antibody fragment binds uniquely to one of rat, porcine, bovine, equine, or ovine TLR9 polypeptide. More specifically, the antibody or antibody fragment binds uniquely to

10   one of the isolated polypeptides of the invention. In one embodiment the antibody or antibody fragment that binds uniquely to one of rat, porcine, bovine, equine, or ovine TLR9 polypeptide also binds to either mouse or human TLR9. In another embodiment the antibody or antibody fragment that binds uniquely to one of rat, porcine, bovine, equine, or ovine TLR9 polypeptide does not also bind to either mouse or human TLR9. In some embodiments

15   the antibody or antibody fragment binds selectively to a chimeric TLR9 polypeptide of the invention. In certain embodiments the antibody or antibody fragment of the invention is a monoclonal antibody or fragment of a monoclonal antibody.

In one aspect the invention provides a method for identifying key amino acids in a TLR9 of a first species which confer specificity for CpG DNA optimized for TLR9 of the

20   first species. The method involves aligning protein sequences of TLR9 of a first species, TLR9 of a second species, and TLR9 of a third species, wherein the TLR9 of the third species preferentially generates a signal when contacted with a CpG DNA optimized for TLR9 of the first species rather than when contacted with a CpG DNA optimized for TLR9 of the second species; generating an initial set of candidate amino acids in the TLR9 of the

25   first species by excluding each amino acid in the TLR9 of the first species which (a) is identical with the TLR9 of the second species or (b) differs from the TLR9 of the second species only by conservative amino acid substitution; generating a refined set of candidate amino acids by selecting each amino acid in the initial set of candidate amino acids in the TLR9 of the first species which (a) is identical with the TLR9 of the third species or (b)

30   differs from the TLR9 of the third species only by conservative amino acid substitution; and identifying as key amino acids in the TLR9 of the first species each amino acid in the refined set of candidate amino acids.

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In another aspect the invention provides a method for identifying key amino acids in human TLR9 which confer specificity for CpG DNA optimized for human TLR9. The method according to this aspect of the invention involves aligning protein sequences of human TLR9, murine TLR9, and TLR9 of a third species, wherein the TLR9 of the third

5   species preferentially generates a signal when contacted with a CpG DNA optimized for human TLR9 rather than when contacted with a CpG DNA optimized for murine TLR9; generating an initial set of candidate amino acids in human TLR9 by excluding each amino acid in human TLR9 which (a) is identical with murine TLR9 or (b) differs from murine TLR9 only by conservative amino acid substitution; generating a refined set of candidate

10 amino acids by selecting each amino acid in the initial set of candidate amino acids in human TLR9 which (a) is identical with the TLR9 of the third species or (b) differs from the TLR9 of the third species only by conservative amino acid substitution; and identifying as key amino acids in human TLR9 each amino acid in the refined set of candidate amino acids. In one embodiment the method according to this aspect of the invention is performed iteratively

15 with a plurality of TLR9s derived from different species other than human and mouse, wherein for each TLR9 the refined set of candidate amino acids is assigned a weight corresponding to a ratio equal to (responsiveness to human-preferred CpG DNA)/(responsiveness to murine-preferred CpG DNA).

In another aspect the invention also provides an isolated polypeptide having an amino

20 acid sequence identical to SEQ ID NO:30 (extracellular domain (ECD) of murine TLR9) except for substitution of at least one key amino acid identified according to the method above. The polypeptide according to this aspect of the invention is a chimeric TLR9 polypeptide. Preferably the polypeptide according to this aspect of the invention binds to CpG DNA optimized for human TLR9 better than does the isolated polypeptide having an

25 amino acid sequence identical to SEQ ID NO:30 (ECD of murine TLR9). In one embodiment the polypeptide includes only one substituted amino acid. The isolated polypeptide according to this aspect of the invention may further include sequence involved in TLR/IL-1R signal transduction, e.g., intracellular domain of TLR9 as provided in SEQ ID NOs 29 and 33. For example, in one embodiment a polypeptide according to this aspect of

30 the invention is an isolated polypeptide having an amino acid sequence identical to SEQ ID NO:29 (full length murine TLR9) except for substitution of at least one key amino acid identified according to the method above.

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In another aspect the invention provides an isolated nucleic acid molecule including a nucleic acid sequence encoding a chimeric TLR9 polypeptide just described. In one embodiment the isolated nucleic acid molecule has a nucleic acid sequence encoding a chimeric TLR9 polypeptide just described.

5 In yet another aspect, the invention provides a screening method to identify a TLR9 ligand. The method involves contacting a polypeptide (including a chimeric TLR9 polypeptide) of the invention with a candidate TLR9 ligand; measuring a signal in response to the contacting; and identifying the candidate TLR9 ligand as a TLR9 ligand when the signal in response to the contacting is consistent with TLR9 signaling. In one embodiment

10 the candidate TLR9 ligand is an immunostimulatory nucleic acid. In one embodiment the candidate TLR9 ligand is a CpG DNA.

The invention also provides, in yet a further aspect, a screening method to identify species-specific CpG-motif preference of an isolated polypeptide of the invention. The method according to this aspect of the invention involves contacting an isolated polypeptide

15 of the invention with a CpG DNA including a hexamer sequence selected from the group consisting of GACGTT, AACGTT, CACGTT, TACGTT, GGCGTT, GCCGTT, GTCGTT, GATGTT, GAAGTT, GAGGTT, GACATT, GACCTT, GACTTT, GACGCT, GACGAT, GACGGT, GACGTC, GACGTA, and GACGTG; measuring a signal in response to the contacting; and identifying a species-specific CpG-motif preference when the signal in

20 response to the contacting is consistent with TLR9 signaling. In one embodiment the CpG DNA is an oligodeoxynucleotide having a sequence selected from the group consisting of

TCCATGACGTTTTTGATGTT	(SEQ ID NO:39),
TCCATAACGTTTTTGATGTT	(SEQ ID NO:40),
TCCATCACGTTTTTGATGTT	(SEQ ID NO:41),
TCCATTACGTTTTTGATGTT	(SEQ ID NO:42),
TCCATGGCGTTTTTGATGTT	(SEQ ID NO:43),
TCCATGCCGTTTTTGATGTT	(SEQ ID NO:44),
TCCATGTCGTTTTTGATGTT	(SEQ ID NO:45),
TCCATGATGTTTTTGATGTT	(SEQ ID NO:46),
TCCATGAAGTTTTTGATGTT	(SEQ ID NO:47),
TCCATGAGGTTTTTGATGTT	(SEQ ID NO:48),
TCCATGACATTTTTGATGTT	(SEQ ID NO:49),
TCCATGACCTTTTTGATGTT	(SEQ ID NO:50),
TCCATGACTTTTTTGATGTT	(SEQ ID NO:51),
TCCATGACGCTTTTGATGTT	(SEQ ID NO:52),
TCCATGACGATTTTGATGTT	(SEQ ID NO:53),
TCCATGACGGTTTTGATGTT	(SEQ ID NO:54),

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TCCATGACGTCTTTGATGTT   (SEQ ID NO:55),
TCCATGACGTATTTGATGTT   (SEQ ID NO:56), and
TCCATGACGTGTTTGATGTT   (SEQ ID NO:57).

In certain embodiments of the screening methods of the invention, the signal includes expression of a reporter gene responsive to TLR/IL-1R signal transduction pathway. In one embodiment the reporter gene is operatively linked to a promoter sensitive to NF-κB. In one embodiment the signal in response to contacting is binding of the candidate TLR9 ligand or CpG DNA to the polypeptide of the invention.

In one embodiment the screening method is performed on a plurality of test compounds. In one embodiment the response mediated by the TLR9 signal transduction pathway is measured quantitatively and the response mediated by the TLR9 signal transduction pathway associated with each of the plurality of test compounds is compared with a response arising as a result of an interaction between the functional TLR9 and a reference immunostimulatory compound.

Brief Description of the Figures

Figure 1 depicts a Clustal W multiple sequence alignment of deduced amino acid sequences for cat (feline), dog (canine), cow (bovine), mouse (murine), sheep (ovine), pig (porcine), horse (equine), human, and rat TLR9 polypeptides. The deduced amino acid sequences for feline, canine, bovine, murine, ovine, porcine, equine, human, and rat TLR9 polypeptides shown in the figure correspond to SEQ ID NOs 25, 21, 9, 29, 17, 5, 13, 33, and 1, respectively. Lines labeled "multiple" refer to the multiple sequence alignment of all six sequences shown. Lines labeled "mo/hu" refer to a paired sequence alignment of mouse and human TLR9 sequences alone.

Figure 2 is a cladogram depicting an evolutionary relatedness tree for rat, murine, porcine, bovine, equine, and human TLR9 polypeptides in Figure 1.

Figure 3 is a graph depicting species specificity of TLR9 signaling with selected oligonucleotides having strong specificity for human (2006), mouse (5890), or neither (1982).

Detailed Description of the Invention

The present invention provides novel amino acid and nucleotide sequences for TLR9 derived from rat, pig, cow, horse, and sheep. These sequences can be used to identify key features of the primary sequences of these and related TLR molecules, including previously

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known primary sequences of human and mouse (murine) TLR9. Such key features include binding site information and species specificity toward particular CpG motifs. Native and novel chimeric TLR9 polypeptides designed with the aid of this information can be expressed in vitro or in vivo and used in screening assays to identify and to design novel TLR9 ligands.

5   Additionally, the native and novel chimeric TLR9 polypeptides designed with the aid of this information can be expressed in vitro or in vivo and used in screening assays to compare various TLR9 ligands, including CpG DNA.

In one aspect the invention provides isolated TLR9 polypeptides, and isolated nucleic acid molecules encoding them, from rat, pig, cow, horse, and sheep. The term "isolated" as

10   used herein with reference to a nucleic acid molecule or polypeptide means substantially free of or separated from components with which it is normally associated in nature, e.g., other nucleic acids, proteins, lipids, carbohydrates or *in vivo* systems to an extent practical and appropriate for its intended use. In particular, the nucleic acids or polypeptides are sufficiently pure and are sufficiently free from other biological constituents of host cells so as

15   to be useful in, for example, producing pharmaceutical preparations. Because an isolated nucleic acid or polypeptide of the invention may be admixed with a pharmaceutically acceptable carrier in a pharmaceutical preparation, the nucleic acid or polypeptide may represent only a small percentage by weight of such a preparation. The nucleic acid or polypeptide is nonetheless substantially pure in that it has been substantially separated from

20   the substances with which it may be associated in living systems.

An amino acid sequence of rat TLR9 is provided as SEQ ID NO:1. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:1 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of rat TLR9 (See

25   Figure 1). Amino acids numbered 1-821 of SEQ ID NO:1 are presumptively extracellular domain and correspond to SEQ ID NO:2. SEQ ID NO:3 is a nucleotide sequence of rat TLR9 cDNA having an open reading frame corresponding to nucleotides 1-3096. SEQ ID NO:4 is a nucleotide sequence of rat cDNA encoding amino acids 1-821 of SEQ ID NO:1.

An amino acid sequence of porcine TLR9 is provided as SEQ ID NO:5. Based on

30   comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:5 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of porcine TLR9

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(See Figure 1). Amino acids numbered 1-819 of SEQ ID NO:5 are presumptively extracellular domain and correspond to SEQ ID NO:6. SEQ ID NO:7 is a nucleotide sequence of porcine TLR9 cDNA having an open reading frame corresponding to nucleotides 77-3166. SEQ ID NO:8 is a nucleotide sequence of porcine cDNA encoding amino acids 1-

5   819 of SEQ ID NO:5.

An amino acid sequence of bovine TLR9 is provided as SEQ ID NO:9. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:9 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of bovine TLR9

10   (See Figure 1). Amino acids numbered 1-818 of SEQ ID NO:9 are presumptively extracellular domain and correspond to SEQ ID NO:10. SEQ ID NO:11 is a nucleotide sequence of bovine TLR9 cDNA having an open reading frame corresponding to nucleotides 84-3170. SEQ ID NO:12 is a nucleotide sequence of bovine cDNA encoding amino acids 1-818 of SEQ ID NO:9.

15   An amino acid sequence of equine TLR9 is provided as SEQ ID NO:13. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:13 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of equine TLR9 (See Figure 1). Amino acids numbered 1-820 of SEQ ID NO:13 are presumptively

20   extracellular domain and correspond to SEQ ID NO:14. SEQ ID NO:15 is a nucleotide sequence of equine TLR9 cDNA having an open reading frame corresponding to nucleotides 115-3207. SEQ ID NO:16 is a nucleotide sequence of equine cDNA encoding amino acids 1-820 of SEQ ID NO:13.

An amino acid sequence of ovine TLR9 is provided as SEQ ID NO:17. Based on

25   comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:17 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of ovine TLR9 (See Figure 1). Amino acids numbered 1-818 of SEQ ID NO:17 are presumptively extracellular domain and correspond to SEQ ID NO:18. SEQ ID NO:19 is a nucleotide sequence of ovine

30   TLR9 cDNA having an open reading frame corresponding to nucleotides 92-3178. SEQ ID NO:20 is a nucleotide sequence of ovine cDNA encoding amino acids 1-818 of SEQ ID NO:17.

SEQ ID NO:1 (Rat TLR9)

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MVLCRRTLHPLSLLVQAAVLAEALALGTLPAFLPCELKPHGLVDCNWLFLKSVPHFSAAEPRSNITSLSLIANRI
HHLHNLDFVHLPNVRQLNLKWNCPPPGLSPLHFSCRMTIEPKTFLAMRMLEELNLSYNGITTVPRLPSSLTNLSL
SHTNILVLDASSLAGLHSLRVLFMDGNCYYKNPCNGAVNVTPDAFLGLSNLTHLSLKYNNLTEVPRQLPPSLEYL
LLSYNLIVKLGAEDLANLTSLRMLDVGGNCRRCDHAPDLCTECRQKSLDLHPQTFHHLSHLEGLVLKDSSLHSLN
SKWFQGLANLSVLDLSENFLYESINKTSAFQNLTRLRKLDLSFNYCKKVSFARLHLASSFKSLVSLQELNMNGIF
FRLLNKNTLRWLAGLPKLHTLHLQMNFINQAQLSVFSTFRALRFVDLSNNRISGPPTLSRVAPEKADEAEKGVPW
PASLTPALPSTPVSKNFMVRCKNLRFTMDLSRNNQVTIKPEMFVNLSHLQCLSLSHNCIAQAVNGSQFLPLTNLK
VLDLSYNKLDLYHSKSFSELPQLQALDLSYNSQPFSMQGIGHNFSFLANLSRLQNLSLAHNDIHSRVSSRLYSTS
VEYLDFSGNGVGRMWDEEDLYLYFFQDLRSLIHLDLSQNKLHILRPQNLNYLPKSLTKLSFRDNHLSFFNWSSLA
FLPNLRDLDLAGNLLKALTNGTLPNGTLLQKLDVSSNSIVFVVPAFFALAVELKEVNLSHNILKTVDRSWFGPIV
MNLTVLDVSSNPLHCACGAPFVDLLLEVQTKVPGLANGVKCGSPRQLQGRSIFAQDLRLCLDDVLSRDCFGLSLL
AVAVGTVLPLLQHLCGWDVWYCFHLCLAWLPLLTRGRRSAQALPYDAFVVFDKAQSAVADWVYNELRVRLEERRG
RRALRLCLEDRDWLPGQTLFENLWASIYGSRKTLFVLAHTDKVSGLLRTSFLLAQQRLLEDRKDVVVLVILRPDA
HRSRYVRLRQRLCRQSVLFWPHQPNGQGSFWAQLSTALTRDNHHFYNRNFCRGPTAE
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SEQ ID NO:2 (Rat TLR9)

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MVLCRRTLHPLSLLVQAAVLAEALALGTLPAFLPCELKPHGLVDCNWLFLKSVPHFSAAEPRSNITSLSLIANRI
HHLHNLDFVHLPNVRQLNLKWNCPPPGLSPLHFSCRMTIEPKTFLAMRMLEELNLSYNGITTVPRLPSSLTNLSL
SHTNILVLDASSLAGLHSLRVLFMDGNCYYKNPCNGAVNVTPDAFLGLSNLTHLSLKYNNLTEVPRQLPPSLEYL
LLSYNLIVKLGAEDLANLTSLRMLDVGGNCRRCDHAPDLCTECRQKSLDLHPQTFHHLSHLEGLVLKDSSLHSLN
SKWFQGLANLSVLDLSENFLYESINKTSAFQNLTRLRKLDLSFNYCKKVSFARLHLASSFKSLVSLQELNMNGIF
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PASLTPALPSTPVSKNFMVRCKNLRFTMDLSRNNQVTIKPEMFVNLSHLQCLSLSHNCIAQAVNGSQFLPLTNLK
VLDLSYNKLDLYHSKSFSELPQLQALDLSYNSQPFSMQGIGHNFSFLANLSRLQNLSLAHNDIHSRVSSRLYSTS
VEYLDFSGNGVGRMWDEEDLYLYFFQDLRSLIHLDLSQNKLHILRPQNLNYLPKSLTKLSFRDNHLSFFNWSSLA
FLPNLRDLDLAGNLLKALTNGTLPNGTLLQKLDVSSNSIVFVVPAFFALAVELKEVNLSHNILKTVDRSWFGPIV
MNLTVLDVSSNPLHCACGAPFVDLLLEVQTKVPGLANGVKCGSPRQLQGRSIFAQDLRLCLDDVLSRDCFG
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SEQ ID NO:3 (Rat TLR9)

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- 10 -

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SEQ ID NO:4 (Rat TLR9)

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SEQ ID NO:5 (Porcine TLR9)

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SEQ ID NO:6 (Porcine TLR9)

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SEQ ID NO:7 (Porcine TLR9)

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- 12 -

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SEQ ID NO:8 (Porcine TLR9)

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SEQ ID NO:9 (Bovine TLR9)

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SEQ ID NO:10 (Bovine TLR9)

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SEQ ID NO:11 (Bovine TLR9)

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SEQ ID NO:12 (Bovine TLR9).

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SEQ ID NO:13 (Equine TLR9)

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SEQ ID NO:14 (Equine TLR9)

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SEQ ID NO:15 (Equine TLR9)

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SEQ ID NO:16 (Equine TLR9)

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SEQ ID NO:17 (Ovine TLR9)

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LSYNHIITLAPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLEK
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10   RSLTNTTLRPLTQLPKLQSLSLSLQLNFINQAELSIFGAFPSLLFVDLSDNRISGAARPVAALGEVDSGVEVWRWPR
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QLEALDLAGNQLKALSNGSLPPGTRLQKLDVSSNSIGFVTPGFFVLANRLKELNLSANALKTVDPFWFGRLTETL
15   NILDVSANPLHCACGAAFVDFLLEMQAAVPGLSRRVTCGSPGQLQGRSIFAQDLRLCLDETLSLDCFGFSLLMVA
LGLAVPMLHHLCGWDLWYCFHLCLAHLPRRRQRGEDTLLYDAFVVFDKAQSAVADWVYNELRVQLEERRGRRAL
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SEQ ID NO:18 (Ovine TLR9)

20

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25   DWFRGLGRLQVLDLSENFLYDYITKTTIFRNLTQLRRLNLSFNYHKKVSFAHLQLAPSFGGLVSLEKLDMHGIFF
RSLTNTTLRPLTQLPKLQSLSLSLQLNFINQAELSIFGAFPSLLFVDLSDNRISGAARPVAALGEVDSGVEVWRWPR
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·LSYNKLDLYHGRSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSASLRA
·LDFSGNSLSQMWAEGDLYLCFFKGLRNLVQLDLSKNHLHTLLPRHLDNLPKSLRQLRLRDNNLAFFNWSSLTVLP
30   ·QLEALDLAGNQLKALSNGSLPPGTRLQKLDVSSNSIGFVTPGFFVLANRLKELNLSANALKTVDPFWFGRLTETL
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SEQ ID NO:19 (Ovine TLR9)

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SEQ ID NO:20 (Ovine TLR9)

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Complete nucleotide and amino acid sequences for canine and feline TLR9 are

5   publicly availiable. For example, an amino acid sequence for canine TLR9 is available as

GenBank accession number BAC65192 and its corresponding nucleotide sequence is

available as GenBank accession number AB104899. An amino acid sequence for feline

TLR9 is available as GenBank accession number AAN15751 and its corresponding

nucleotide sequence is available as GenBank accession number AY137581.

10 Complete nucleotide and amino acid sequences for canine and feline TLR9 were also

determined independently from those available from public databases.

An amino acid sequence of canine TLR9 is provided as SEQ ID NO:21. Based on

comparison with known amino acid sequences of human and murine TLR9, it appears that

SEQ ID NO:21 includes sequence for at least a majority of the extracellular domain, all of the

15 transmembrane domain, and at least a portion of the intracellular domain of canine TLR9

(See Figure 1). Amino acids numbered 1-822 of SEQ ID NO:21 are presumptively

extracellular domain and correspond to SEQ ID NO:22. SEQ ID NO:23 is a nucleotide

sequence of canine TLR9 cDNA having an open reading frame corresponding to nucleotides

91-3186. SEQ ID NO:24 is a nucleotide sequence of canine cDNA encoding amino acids 1-

20 822 of SEQ ID NO:21.

An amino acid sequence of feline TLR9 is provided as SEQ ID NO:25. Based on

comparison with known amino acid sequences of human and murine TLR9, it appears that

SEQ ID NO:25 includes sequence for at least a majority of the extracellular domain, all of the

transmembrane domain, and at least a portion of the intracellular domain of feline TLR9 (See

25 Figure 1). Amino acids numbered 1-820 of SEQ ID NO:25 are presumptively extracellular

domain and correspond to SEQ ID NO:26. SEQ ID NO:27 is a nucleotide sequence of feline

TLR9 cDNA having an open reading frame corresponding to nucleotides 87-3179. SEQ ID

NO:28 is a nucleotide sequence of feline cDNA encoding amino acids 1-820 of SEQ ID

NO:25.

30

SEQ ID NO:21 (Canine TLR9)

MGPCRGALHPLSLLVQAAALALALAQGTLPAFLPCELQPHGLVNCNWLFLKSVPRFSAAAPRGNVTSLSLYSNRI
HHLHDYDFVHFVHLRRLNLKWNCPPASLSPMHFPCHMTIEPNTFLAVPTLEDLNLSYNSITTVPALPSSLVSLSL
SRTNILVLDPATLAGLYALRFLFLDGNCYYKNPCQQALQVAPGALLGLGNLTHLSLKYNNLTVVPRGLPPSLEYL

- 20 -

LLSYNHIITLAPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKGFPQLHPNTFGHLSHLEGLVLRDSSLYSLD
PRWFHGLGNLMVLDLSENFLYDCITKTKAFYGLARLRRLNLSFNYHKKVSFAHLHLASSFGSLLSLQELDIHGIF
FRSLSKTTLQSLAHLPMLQRLHLQLNFISQAQLSIFGAFPGLRYVDLSDNRISGAAEPAAATGEVEADCGERVWP
QSRDLALGPLGTPGSEAFMPSCRTLNFTLDLSRNNLVTVQPEMFVRLARLQCLGLSHNSISQAVNGSQFVPLSNL
5   RVLDLSHNKLDLYHGRSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA
SLRALDFSGNTLSQMWAEGDLYLRFFQGLRSLVQLDLSQNRLHTLLPRNLDNLPKSLRLLRLRDNYLAFFNWSSL
ALLPKLEALDLAGNQLKALSNGSLPNGTQLQRLDLSGNSIGFVVPSFFALAVRLRELNLSANALKTVEPSWFGSL
AGALKVLDVTANPLHCACGATFVDFLLEVQAAVPGLPSRVKCGSPGQLQGRSIFAQDLRLCLDEALSWVCFSLSL
LAVALSLAVPMLHQLCGWDLWYCFHLCLAWLPRRGRRRGVDALAYDAFVVFDKAQSSVADWVYNELRVQLEERRG
10   RRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRLLEDRKDVVVLVILCPDA
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SEQ ID NO:22 (Canine TLR9)

MGPCRGALHPLSLLVQAAALALALAQGTLPAFLPCELQPHGLVNCNWLFLKSVPRFSAAAPRGNVTSLSLYSNRI
15   HHLHDYDFVHFVHLRRLNLKWNCPPASLSPMHFPCHMTIEPNTFLAVPTLEDLNLSYNSITTVPALPSSLVSLSL
SRTNILVLDPATLAGLYALRFLFLDGNCYYKNPCQQALQVAPGALLGLGNLTHLSLKYNNLTVVPRGLPPSLEYL
LLSYNHIITLAPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKGFPQLHPNTFGHLSHLEGLVLRDSSLYSLD
PRWFHGLGNLMVLDLSENFLYDCITKTKAFYGLARLRRLNLSFNYHKKVSFAHLHLASSFGSLLSLQELDIHGIF
FRSLSKTTLQSLAHLPMLQRLHLQLNFISQAQLSIFGAFPGLRYVDLSDNRISGAAEPAAATGEVEADCGERVWP
20   QSRDLALGPLGTPGSEAFMPSCRTLNFTLDLSRNNLVTVQPEMFVRLARLQCLGLSHNSISQAVNGSQFVPLSNL
RVLDLSHNKLDLYHGRSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA
SLRALDFSGNTLSQMWAEGDLYLRFFQGLRSLVQLDLSQNRLHTLLPRNLDNLPKSLRLLRLRDNYLAFFNWSSL
ALLPKLEALDLAGNQLKALSNGSLPNGTQLQRLDLSGNSIGFVVPSFFALAVRLRELNLSANALKTVEPSWFGSL
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25

SEQ ID NO:23 (Canine TLR9)

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SEQ ID NO:24 (Canine TLR9)

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SEQ ID NO:25 (Feline TLR9)

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SRTNILVLDPANLAGLHSLRFLFLDGNCYYKNPCPQALQVAPGALLGLGNLTHLSLKYNNLTAVPRGLPPSLEYL
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PRWFHALGNLMVLDLSENFLYDCITKTTAFQGLAQLRRLNLSFNYHKKVSFAHLHLAPSFGSLLSLQQLDMHGIF
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LPRLEALDLAGNQLKALSNGSLPNGTQLQRLDLSSNSISFVASSFFALATRLRELNLSANALKTVEPSWFGSLAG
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SEQ ID NO:26 (Feline TLR9)

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LPRLEALDLAGNQLKALSNGSLPNGTQLQRLDLSSNSISFVASSFFALATRLRELNLSANALKTVEPSWFGSLAG
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SEQ ID NO:27 (Feline TLR9)

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SEQ ID NO:28 (Feline TLR9)

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Complete nucleotide and amino acid sequences for murine and human TLR9 are

publicly available. For example, an amino acid sequence of murine TLR9 is available as

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GenBank accession no. AAK29625, provided as SEQ ID NO:29. Amino acids numbered 1-821 of SEQ ID NO:29 presumptively include the entire extracellular domain and correspond to SEQ ID NO:30. SEQ ID NO:31 corresponds to GenBank accession number AF348140, which is a nucleotide sequence of murine TLR9 cDNA. SEQ ID NO:32 is a nucleotide

5 sequence of murine cDNA encoding amino acids 1-821 of SEQ ID NO:29.

An amino acid sequence of human TLR9 is available as GenBank accession no. AAF78037, provided as SEQ ID NO:33. Amino acids numbered 1-820 of SEQ ID NO:33 presumptively include the entire extracellular domain and correspond to SEQ ID NO:34. SEQ ID NO:35 corresponds to GenBank accession number AF245704, which is a nucleotide

10 sequence of human TLR9 cDNA. SEQ ID NO:36 is a nucleotide sequence of human cDNA encoding amino acids 1-820 of SEQ ID NO:33.

SEQ ID NO:29 (Murine TLR9)

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SEQ ID NO:30 (Murine TLR9)

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SEQ ID NO:31 (Murine TLR9)

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SEQ ID NO:31 (Murine TLR9)

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SEQ ID NO:33 (Human TLR9)

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SEQ ID NO:34 (Human TLR9)

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MGFCRSALHPLSLLVQAIMLAMTLALGTLPAFLPCELQPHGLVNCNWLFLKSVPHFSMAAPRGNVTSLSLSSNRI
HHLHDSDFAHLPSLRHLNLKWNCPPVGLSPMHFPCHMTIEPSTFLAVPTLEELNLSYNNIMTVPALPKSLISLSL
SHTNILMLDSASLAGLHALRFLFMDGNCYYKNPCRQALEVAPGALLGLGNLTHLSLKYNNLTVVPRNLPSSLEYL
LLSYNRIVKLAPEDLANLTALRVLDVGGNCRRCDHAPNPCMECPRHFPQLHPDTFSHLSRLEGLVLKDSSLSWLN
ASWFRGLGNLRVLDLSENFLYKCITKTKAFQGLTQLRKLNLSFNYQKRVSFAHLSLAPSFGSLVALKELDMHGIF
FRSLDETTLRPLARLPMLQTLRLQMNFINQAQLGIFRAFPGLRYVDLSDNRISGASELTATMGEADGGEKVWLQP
GDLAPAPVDTPSSEDFRPNCSTLNFTLDLSRNNLVTVQPEMFAQLSHLQCLRLSHNCISQAVNGSQFLPLTGLQV
LDLSRNKLDLYHEHSFTELPRLEALDLSYNSQPFGMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCSTSL
RALDFSGNALGHMWAEGDLYLHFFQGLSGLIWLDLSQNRLHTLLPQTLRNLPKSLQVLRLRDNYLAFFKWWSLHF
LPKLEVLDLAGNRLKALTNGSLPAGTRLRRLDVSCNSISFVAPGFFSKAKELRELNLSANALKTVDHSWFGPLAS
ALQILDVSANPLHCACGAAFMDFLLEVQAAVPGLPSRVKCGSPGQLQGLSIFAQDLRLCLDEALSWDCFA
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SEQ ID NO:35 (Human TLR9)

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aggctggtataaaaatcttacttcctctattctctgagccgctgctgccctgtgggaagggacctcgagtgtga
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ttctgccgcagcgccctgcacccgctgtctctcctggtgcaggccatcatgctggccatgaccctggccctgggt
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accttgcctgccttcctaccctgtgagctccagccccacggcctggtgaactgcaactggctgttcctgaagtct
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accaacatcctgatgctagactctgccagcctcgccggcctgcatgccctgcgcttcctattcatggacggcaac
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SEQ ID NO:36 (Human TLR9)

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atgggtttctgccgcagcgccctgcacccgctgtctctcctggtgcaggccatcatgctggccatgaccctggcc
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aagtctgtgccccacttctccatggcagcaccccgtggcaatgtcaccagcctttccttgtcctccaaccgcatc
caccacctccatgattctgactttgcccacctgcccagcctgcggcatctcaacctcaagtggaactgcccgccg
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aaaaccaaggccttccagggcctaacacagctgcgcaagcttaacctgtccttcaattaccaaaagagggtgtcc
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cgggccctggacttcagcggcaatgcactgggccatatgtgggccgagggagacctctatctgcacttcttccaa
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gagctgcgagagctcaaccttagcgccaacgccctcaagacagtggaccactcctggtttgggcccctggcgagt
gccctgcaaatactagatgtaagcgccaaccctctgcactgcgcctgtggggcggcctttatggacttcctgctg
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atctttgcacaggacctgcgcctctgcctggatgaggccctctcctgggactgtttcgcc
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In addition to the foregoing native rat, porcine, bovine, equine, and ovine TLR9 polypeptides and nucleic acid molecules encoding them, chimeric TLR9 polypeptides and nucleic acid molecules encoding them are provided by the invention. The chimeric polypeptides include at least one amino acid subsitition based on a comparison of conserved and non-conserved amino acids among at least two of rat, murine, porcine, bovine, equine, ovine, canine, feline, and human TLR9. The information contained in a multiple sequence alignment of these various TLR9 polypeptide sequences, provided for example in Figure 1, can be used to identify and select individual amino acid positions and even individual amino acids to substitute in designing a chimeric TLR9. The substitution or substitutions can be effected using methods known to those of ordinary skill in molecular biology. Nucleic acids encoding the native or chimeric polypeptides of the invention can be inserted into an expression vector and used to express TLR9 polypeptide.

A conservative amino acid substitution shall refer to a substitution of a first amino acid for a second amino acid, wherein side chains of the first amino acid and the second amino acid share similar features in terms of hydrophobicity, size, aromaticity, or tendency to alter conformation. For example, conservative amino acid substitutions generally may be made between members within each of the following groups: hydrophobic (A, I, L, M, V), neutral (C, S, T), acidic (D, E), basic (H, K, N, Q, R), and aromatic (F, W, Y). A non-conservative amino acid substitution refers to any other amino acid substitution.

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An expression vector for TLR9 will include at least a nucleotide sequence coding for a TLR9, or a fragment thereof coding for a functional TLR9 polypeptide, operably linked to a gene expression sequence which can direct the expression of the TLR9 nucleic acid within a eukaryotic or prokaryotic cell. A "gene expression sequence" is any regulatory nucleotide sequence, such as a promoter sequence or promoter-enhancer combination, which facilitates the efficient transcription and translation of the nucleic acid to which it is operably linked. With respect to TLR9 nucleic acid, the "gene expression sequence" is any regulatory nucleotide sequence, such as a promoter sequence or promoter-enhancer combination, which facilitates the efficient transcription and translation of the TLR9 nucleic acid to which it is operably linked. The gene expression sequence may, for example, be a mammalian or viral promoter, such as a constitutive or inducible promoter. Constitutive mammalian promoters include, but are not limited to, the promoters for the following genes: hypoxanthine phosphoribosyl transferase (HPRT), adenosine deaminase, pyruvate kinase, β-actin promoter, and other constitutive promoters. Exemplary viral promoters which function constitutively in eukaryotic cells include, for example, promoters from the simian virus (e.g., SV40), papillomavirus, adenovirus, human immunodeficiency virus (HIV), Rous sarcoma virus (RSV), cytomegalovirus (CMV), the long terminal repeats (LTR) of Moloney murine leukemia virus and other retroviruses, and the thymidine kinase (TK) promoter of herpes simplex virus. Other constitutive promoters are known to those of ordinary skill in the art. The promoters useful as gene expression sequences of the invention also include inducible promoters. Inducible promoters are expressed in the presence of an inducing agent. For example, the metallothionein (MT) promoter is induced to promote transcription and translation in the presence of certain metal ions. Other inducible promoters are known to those of ordinary skill in the art.

In general, the gene expression sequence shall include, as necessary, 5' non-transcribing and 5' non-translating sequences involved with the initiation of transcription and translation, respectively, such as a TATA box, capping sequence, CAAT sequence, and the like. Especially, such 5' non-transcribing sequences will include a promoter region which includes a promoter sequence for transcriptional control of the operably joined nucleic acid coding sequence for a TLR9 polypeptide. The gene expression sequences optionally include enhancer sequences or upstream activator sequences as desired.

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Generally a nucleic acid coding sequence and a gene expression sequence are said to be "operably linked" when they are covalently linked in such a way as to place the transcription and/or translation of the nucleic acid coding sequence under the influence or control of the gene expression sequence. Thus the TLR9 nucleic acid coding sequence and

5   the gene expression sequence are said to be "operably linked" when they are covalently linked in such a way as to place the transcription and/or translation of the TLR9 nucleic acid coding sequence under the influence or control of the gene expression sequence. If it is desired that the TLR9 sequence be translated into a functional protein, two DNA sequences are said to be operably linked if induction of a promoter in the 5' gene expression sequence

10   results in the transcription of the TLR9 sequence and if the nature of the linkage between the two DNA sequences does not (1) result in the introduction of a frame-shift mutation, (2) interfere with the ability of the promoter region to direct the transcription of the TLR9 sequence, or (3) interfere with the ability of the corresponding RNA transcript to be translated into a protein. Thus, a gene expression sequence would be operably linked to a

15   TLR9 nucleic acid sequence if the gene expression sequence were capable of effecting transcription of that TLR9 nucleic acid sequence such that the resulting transcript might be translated into the desired TLR9 protein or polypeptide.

A "TLR9 ligand" as used herein refers to a molecule that specifically binds a TLR9 polypeptide. In one embodiment the TLR9 ligand specifically binds a TLR9 polypeptide

20   corresponding to at least a ligand-binding portion of the extracellular domain of TLR9. In most instances a TLR9 ligand will also induce TLR9 signaling when contacted with TLR9 under suitable conditions. TLR9 signaling refers to TLR/IL-1R signal transduction mediated through the TLR9, as described in further detail elsewhere herein. As mentioned above, CpG nucleic acids have been reported to be TLR9 ligands, but TLR9 ligands may include other

25   entities as well, including, for example, small molecules. As also previously mentioned, there appears to be a species-specific preference for at least certain TLR9s and certain CpG motifs. As used herein, a species-preferred CpG DNA refers to a particular CpG DNA that is optimized for signal induction by a TLR9 of a particular species. A CpG DNA that is optimized for signal induction by a TLR9 of a particular species refers to a CpG DNA having

30   a sequence that preferentially binds to and/or induces signaling by TLR9 of that species. For example, a human-preferred CpG DNA shall refer to a CpG DNA that optimally stimulates human TLR9 to signal through its TIR domain. Likewise, a murine-preferred CpG DNA

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shall refer to a CpG DNA that optimally stimulates murine TLR9 to signal through its TIR domain. Examples of human-preferred and murine-preferred CpG DNA are ODN 2006 (SEQ ID NO:58) and 1668 (SEQ ID NO:60), respectively.

The binding and species specificity of TLR9s are believed to be influenced by key amino acids present in the extracellular domain of TLR9. Key amino acids in a TLR9 as used herein refer to those amino acids which contribute significantly to ligand binding and ligand specificity of a particular TLR9 polypeptide.

A "CpG nucleic acid" or a "CpG immunostimulatory nucleic acid" as used herein is a nucleic acid containing at least one unmethylated CpG dinucleotide (cytosine-guanine dinucleotide sequence, i.e., "CpG DNA" or DNA containing a 5' cytosine followed by 3' guanine and linked by a phosphate bond) which activates a component of the immune system. The entire CpG nucleic acid can be unmethylated or portions may be unmethylated but at least the C of the 5' CG 3' must be unmethylated.

In one embodiment a CpG nucleic acid is represented by at least the formula:

$$5'-N_1X_1CGX_2N_2-3'$$

wherein X_1 and X_2 are nucleotides, N is any nucleotide, and N_1 and N_2 are nucleic acid sequences composed of from about 0-25 N's each. In some embodiments X_1 is adenine, guanine, or thymine and/or X_2 is cytosine, adenine, or thymine. In other embodiments X_1 is cytosine and/or X_2 is guanine.

Nucleic acids having modified backbones, such as phosphorothioate backbones, also fall within the class of immunostimulatory nucleic acids. U.S. Pat. Nos. 5,723,335 and 5,663,153 issued to Hutcherson, et al. and related PCT publication WO95/26204 describe immune stimulation using phosphorothioate oligonucleotide analogues. These patents describe the ability of the phosphorothioate backbone to stimulate an immune response in a non-sequence specific manner.

An immunostimulatory nucleic acid molecule, including for example a CpG DNA, may be double-stranded or single-stranded. Generally, double-stranded molecules may be more stable *in vivo*, while single-stranded molecules may have increased activity. The terms "nucleic acid" and "oligonucleotide" refer to multiple nucleotides (i.e., molecules comprising a sugar (e.g., ribose or deoxyribose) linked to a phosphate group and to an exchangeable organic base, which is either a substituted pyrimidine (e.g., cytosine (C), thymine (T) or uracil (U)) or a substituted purine (e.g., adenine (A) or guanine (G)) or a modified base. As

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used herein, the terms "nucleic acid" and "oligonucleotide" refer to oligoribonucleotides as
well as oligodeoxyribonucleotides. The terms shall also include polynucleosides (i.e., a
polynucleotide minus the phosphate) and any other organic base-containing polymer.   The
terms "nucleic acid" and "oligonucleotide" also encompass nucleic acids or oligonucleotides

5   with a covalently modified base and/or sugar. For example, they include nucleic acids having
backbone sugars which are covalently attached to low molecular weight organic groups other
than a hydroxyl group at the 2' position and other than a phosphate group at the 5' position.
Thus modified nucleic acids may include a 2'-O-alkylated ribose group. In addition,
modified nucleic acids may include sugars such as arabinose instead of ribose. Thus the

10   nucleic acids may be heterogeneous in backbone composition thereby containing any
possible combination of polymer units linked together such as peptide-nucleic acids (which
have amino acid backbone with nucleic acid bases). In some embodiments the nucleic acids
are homogeneous in backbone composition.

The substituted purines and pyrimidines of the immunostimulatory nucleic acids
15   include standard purines and pyrimidines such as cytosine as well as base analogs such as C-
5 propyne substituted bases. Wagner RW et al. (1996) *Nat Biotechnol* 14:840-4. Purines and
pyrimidines include but are not limited to adenine, cytosine, guanine, thymine, 5-
methylcytosine, 2-aminopurine, 2-amino-6-chloropurine, 2,6-diaminopurine, hypoxanthine,
and other naturally and non-naturally occurring nucleobases, substituted and unsubstituted

20   aromatic moieties.

The immunostimulatory nucleic acid is a linked polymer of bases or nucleotides. As
used herein with respect to linked units of a nucleic acid, "linked" or "linkage" means two
entities are bound to one another by any physicochemical means. Any linkage known to
those of ordinary skill in the art, covalent or non-covalent, is embraced. Such linkages are

25   well known to those of ordinary skill in the art. Natural linkages, which are those ordinarily
found in nature connecting the individual units of a nucleic acid, are most common. The
individual units of a nucleic acid may be linked, however, by synthetic or modified linkages.

Whenever a nucleic acid is represented by a sequence of letters it will be understood
that the nucleotides are in 5' to 3' (or equivalent) order from left to right and that "A" denotes

30   adenine, "C" denotes cytosine, "G" denotes guanine, "T" denotes thymidine, and "U" denotes
uracil unless otherwise noted.

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Immunostimulatory nucleic acid molecules useful according to the invention can be obtained from natural nucleic acid sources (e.g., genomic nuclear or mitochondrial DNA or cDNA), or are synthetic (e.g., produced by oligonucleotide synthesis). Nucleic acids isolated from existing nucleic acid sources are referred to herein as native, natural, or isolated nucleic

5   acids. The nucleic acids useful according to the invention may be isolated from any source, including eukaryotic sources, prokaryotic sources, nuclear DNA, mitochondrial DNA, etc. Thus, the term nucleic acid encompasses both synthetic and isolated nucleic acids.

The immunostimulatory nucleic acids can be produced on a large scale in plasmids, (see *Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition,

10   Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989) and separated into smaller pieces or administered whole. After being administered to a subject the plasmid can be degraded into oligonucleotides. One skilled in the art can purify viral, bacterial, eukaryotic, etc. nucleic acids using standard techniques, such as those employing restriction enzymes, exonucleases or endonucleases.

15   For use in the instant invention, the immunostimulatory nucleic acids can be synthesized *de novo* using any of a number of procedures well known in the art. For example, the β-cyanoethyl phosphoramidite method (Beaucage SL and Caruthers MH, *Tetrahedron Let* 22:1859 (1981)); nucleoside H-phosphonate method (Garegg et al., *Tetrahedron Let* 27:4051-4054 (1986); Froehler et al., *Nucl Acid Res* 14:5399-5407 (1986);

20   Garegg et al., *Tetrahedron Let* 27:4055-4058 (1986); Gaffney et al., *Tetrahedron Let* 29:2619-2622 (1988)). These chemistries can be performed by a variety of automated oligonucleotide synthesizers available in the market.

The immunostimulatory nucleic acid may be any size of at least 6 nucleotides but in some embodiments are in the range of between 6 and 100 or in some embodiments between 8

25   and 35 nucleotides in size. Immunostimulatory nucleic acids can be produced on a large scale in plasmids. These may be administered in plasmid form or alternatively they can be degraded into oligonucleotides before administration.

A "stabilized immunostimulatory nucleic acid" shall mean a nucleic acid molecule that is relatively resistant to *in vivo* degradation (e.g., via an exo- or endo-nuclease).

30   Stabilization can be a function of length or secondary structure. Nucleic acids that are tens to hundreds of kbs long are relatively resistant to *in vivo* degradation. For shorter nucleic acids, secondary structure can stabilize and increase their effect. For example, if the 3' end of an

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oligonucleotide has self-complementarity to an upstream region, so that it can fold back and form a sort of stem loop structure, then the oligonucleotide becomes stabilized and therefore exhibits more activity.

Some stabilized immunostimulatory nucleic acids have a modified backbone. It has been demonstrated that modification of the oligonucleotide backbone provides enhanced activity of the immunostimulatory nucleic acids when administered *in vivo*. Nucleic acids, including at least two phosphorothioate linkages at the 5' end of the oligonucleotide and multiple phosphorothioate linkages at the 3' end, preferably 5, may provide maximal activity and protect the oligonucleotide from degradation by intracellular exo- and endo-nucleases. Other modified oligonucleotides include phosphodiester modified oligonucleotide, combinations of phosphodiester and phosphorothioate oligonucleotide, methylphosphonate, methylphosphorothioate, phosphorodithioate, and combinations thereof. Each of these combinations and their particular effects on immune cells is discussed in more detail in U.S. Pat. Nos. 6,194,388 and 6,207,646, the entire contents of which are incorporated herein by reference. It is believed that these modified oligonucleotides may show more stimulatory activity due to enhanced nuclease resistance, increased cellular uptake, increased protein binding, and/or altered intracellular localization. Both phosphorothioate and phosphodiester nucleic acids are active in immune cells.

Other stabilized immunostimulatory nucleic acids include: nonionic DNA analogs, such as alkyl- and aryl-phosphates (in which the charged phosphonate oxygen is replaced by an alkyl or aryl group), phosphodiester and alkylphosphotriesters, in which the charged oxygen moiety is alkylated. Oligonucleotides which contain diol, such as tetraethyleneglycol or hexaethyleneglycol, at either or both termini have also been shown to be substantially resistant to nuclease degradation.

Phosphorothioate nucleic acid molecules may be synthesized using automated techniques employing either phosphoramidate or H-phosphonate chemistries. Aryl- and alkyl-phosphonates can be made, e.g., as described in U.S. Pat. No. 4,469,863; and alkylphosphotriesters (in which the charged oxygen moiety is alkylated as described in U.S. Pat. No. 5,023,243 and European Patent No. 092,574) can be prepared by automated solid phase synthesis using commercially available reagents. Methods for making other DNA backbone modifications and substitutions have been described. Uhlmann E and Peyman A (1990) *Chem Rev* 90:544; Goodchild J (1990) *Bioconjugate Chem* 1:165.

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Other sources of immunostimulatory nucleic acids useful according to the invention include standard viral and bacterial vectors, many of which are commercially available. In its broadest sense, a "vector" is any nucleic acid material which is ordinarily used to deliver and facilitate the transfer of nucleic acids to cells. The vector as used herein may be an empty vector or a vector carrying a gene which can be expressed. In the case when the vector is carrying a gene the vector generally transports the gene to the target cells with reduced degradation relative to the extent of degradation that would result in the absence of the vector. In this case the vector optionally includes gene expression sequences to enhance expression of the gene in target cells such as immune cells, but it is not required that the gene be expressed in the cell.

Nucleic acid-binding fragments of TLRs are believed to include the extracytoplasmic (extracellular) domain or subportions thereof, such as those which include at least an MBD motif, a CXXC motif, or both an MBD motif and a CXXC motif.

Both mouse and human TLR9 have an N-terminal extension of approximately 180 amino acids compared to other TLRs. An insertion also occurs at amino acids 253-268, which is not found in TLRs 1-6 but is present in human TLR7 and human TLR8. This insert has two CXXC motifs which participate in forming a CXXC domain. The CXXC domain resembles a zinc finger motif and is found in DNA-binding proteins and in certain specific CpG binding proteins, e.g., methyl-CpG binding protein-1 (MBD-1). Fujita N et al. (2000) *Mol Cell Biol* 20:5107-18. Both human and mouse TLR9 CXXC domains occur at aa 253-268:

CXXC motif:	GNCXXCXXXXXXCXXC	SEQ ID NO:62
Human TLR9:	GNCRRCDHAPNPCMEC	SEQ ID NO:63
Murine TLR9:	GNCRRCDHAPNPCMIC	SEQ ID NO:64

An additional motif believed to be involved in CpG binding is the MBD motif, also found in MBD-1, listed below as SEQ ID NO:53. Fujita, N et al.(2000) *Mol Cell Biol* 20:5107-18; Ohki I et al. (1999) *EMBO J* 18:6653-61. Amino acids 524-554 of hTLR9 and aa 525-555 of mTLR9 correspond to the MBD motif of MBD-1 as shown:

MBD motif:

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MBD-1   R-XXXXXXX-R-X-D-X-Y-XXXXXXXXX-R-S-XXXXX-Y   SEQ ID NO:65
hTLR9   Q-XXXXXXX-K-X-D-X-Y-XXXXXXXXX-R-L-XXXXX-Y   SEQ ID NO:66
mTLR9   Q-XXXXXXX-K-X-D-X-Y-XXXXXXXXX-Q-L-XXXXX-Y   SEQ ID NO:67

5   hTLR9   Q-VLDLSRN-K-L-D-L-Y-HEHSFTELP-R-L-EALDLS-Y   SEQ ID NO:68
     mTLR9   Q-VLDLSHN-K-L-D-L-Y-HWKSFSELP-Q-L-QALDLS-Y   SEQ ID NO:69

Although the signaling functions of MBD-1 and TLR9 are quite different, the core D-X-Y is conserved and is believed to be involved in CpG binding.

10   According to another aspect of the invention, a screening method is provided for identifying an immunostimulatory compound. The method according to this aspect of the invention involves contacting a functional TLR9 with a test compound; detecting presence or absence of a response mediated by a TLR9 signal transduction pathway in the presence of the test compound arising as a result of an interaction between the functional TLR9 and the test

15   compound; and determining the test compound is an immunostimulatory compound when the presence of a response mediated by the TLR9 signal transduction pathway is detected.

An immunostimulatory compound is a natural or synthetic compound that is capable of inducing an immune response when contacted with an immune cell. A TLR9 ligand that is an immunostimulatory compound is a natural or synthetic compound that is capable of

20   inducing an immune response when contacted with an immune cell that expresses TLR9. A TLR9 ligand that is an immunostimulatory compound is also a natural or synthetic compound that is capable of inducing a TLR/IL-1R signal transduction pathway when contacted with a TLR9. Immunostimulatory compounds include but are not limited to immunostimulatory nucleic acids. The immunostimulatory compound can be, for example, a nucleic acid

25   molecule, polynucleotide or oligonucleotide, a polypeptide or oligopeptide, a lipid or lipopolysaccharide, a small molecule.

A basis for certain of the screening assays is the presence of a functional TLR9 in a cell. The functional TLR9 in some instances is naturally expressed by a cell. In other instances, expression of the functional TLR9 can involve introduction or reconstitution of a

30   species-specific TLR9 into a cell or cell line that otherwise lacks the TLR9 or lacks responsiveness to immunostimulatory nucleic acid, resulting in a cell or cell line capable of activating the TLR/IL-1R signaling pathway in response to contact with an

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immunostimulatory nucleic acid. In yet other instances, expression of the functional TLR9
can involve introduction of a chimeric or modified TLR9 into a cell or cell line that otherwise
lacks the TLR9 or lacks responsiveness to immunostimulatory nucleic acid, resulting in a cell
or cell line capable of activating the TLR/IL-1R signaling pathway in response to contact
5   with an immunostimulatory nucleic acid. Examples of cell lines lacking TLR9 or
immunostimulatory nucleic acid responsiveness include, but are not limited to, 293
fibroblasts (ATCC CRL-1573), MonoMac-6, THP-1, U937, CHO, and any TLR9 knock-out.
The introduction of the species-specific, chimeric or modified TLR9 into the cell or cell line
is preferably accomplished by transient or stable transfection of the cell or cell line with a
10   TLR9-encoding nucleic acid sequence operatively linked to a gene expression sequence (as
described above). Methods for transient and for stable transfection of a cell are well known
in the art.

　　　　The screening assays can have any of a number of possible readout systems based
upon either TLR/IL-1R signaling pathway or other assays useful for assessing response to
15   immunostimulatory nucleic acids. It has been reported that immune cell activation by CpG
immunostimulatory sequences is dependent in some way on endosomal processing.

　　　　In certain embodiments, the readout for the screening assay is based on the use of
native genes or, alternatively, cotransfected or otherwise co-introduced reporter gene
constructs which are responsive to the TLR/IL-1R signal transduction pathway involving
20   MyD88, TRAF, p38, and/or ERK. Häcker H et al. (1999) *EMBO J* 18:6973-6982. These
pathways activate kinases including κB kinase complex and c-Jun N-terminal kinases. Thus
reporter genes and reporter gene constructs particularly useful for the assays can include a
reporter gene operatively linked to a promoter sensitive to NF-κB. Examples of such
promoters include, without limitation, those for NF-κB, IL-1β, IL-6, IL-8, IL-12 p40, CD80,
25   CD86, and TNF-α. The reporter gene operatively linked to the TLR-sensitive promoter can
include, without limitation, an enzyme (e.g., luciferase, alkaline phosphatase, β-galactosidase,
chloramphenicol acetyltransferase (CAT), etc.), a bioluminescence marker (e.g., green-
fluorescent protein (GFP, U.S. Pat. No. 5,491,084), blue fluorescent protein, etc.), a surface-
expressed molecule (e.g., CD25), and a secreted molecule (e.g., IL-8, IL-12 p40, TNF-α). In
30   certain embodiments the reporter is selected from IL-8, TNF-α, NF-κB-luciferase (NF-κB-
luc; Häcker H et al. (1999) *EMBO J* 18:6973-6982), IL-12 p40-luc (Murphy TL et al. (1995)

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Mol Cell Biol 15:5258-5267), and TNF-luc (Häcker H et al. (1999) *EMBO J* 18:6973-6982).

At least one of these reporter constructs (NF-κB-luc) is commercially available (Stratagene,

La Jolla, CA). In assays relying on enzyme activity readout, substrate can be supplied as part

of the assay, and detection can involve measurement of chemiluminescence, fluorescence,

5   color development, incorporation of radioactive label, drug resistance, or other marker of

enzyme activity. For assays relying on surface expression of a molecule, detection can be

accomplished using FACS analysis or functional assays. Secreted molecules can be assayed

using enzyme-linked immunosorbent assay (ELISA) or bioassays. Many such readout

systems are well known in the art and are commercially available.

10   According to one embodiment of this method, comparison can be made to a reference

immunostimulatory nucleic acid. The reference immunostimulatory nucleic acid may be any

suitably selected immunostimulatory nucleic acid, including a CpG nucleic acid. In certain

embodiments the screening method is performed using a plurality of test nucleic acids. In

certain embodiments comparison of test and reference responses is based on comparison of

15   quantitative measurements of responses in each instance.

               In another aspect the invention provides a screening method for identifying species

specificity of an immunostimulatory nucleic acid. The method involves contacting a TLR9

of a first species with a test immunostimulatory nucleic acid; contacting a TLR9 of a second

species with the test immunostimulatory nucleic acid; measuring a response mediated by a

20   TLR signal transduction pathway associated with the contacting the TLR9 of the first species

with the test immunostimulatory nucleic acid; measuring a response mediated by the TLR

signal transduction pathway associated with the contacting the TLR9 of the second species

with the test immunostimulatory nucleic acid; and comparing the two responses. The TLR9

may be expressed by a cell or it may be part of a cell-free system. The TLR9 may be part of

25   a complex, with either another TLR or with another protein, e.g., MyD88, IRAK, TRAF,

IκB, NF-κB, or functional homologues and derivatives thereof. Thus for example a given

ODN can be tested against a panel of human fibroblast 293 fibroblast cells transfected with

TLR9 from various species and optionally cotransfected with a reporter construct sensitive to

TLR/IL-1R activation pathways. Thus in another aspect, the invention provides a method for

30   screening species selectivity with respect to a given nucleic acid sequence.

               Test compounds can include but are not limited to peptide nucleic acids (PNAs),

antibodies, polypeptides, carbohydrates, lipids, hormones, and small molecules. Test

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compounds can further include variants of a reference immunostimulatory nucleic acid incorporating any one or combination of the substitutions described above. Test compounds can be generated as members of a combinatorial library of compounds.

In preferred embodiments, the screening methods can be performed on a large scale and with high throughput by incorporating, e.g., an array-based assay system and at least one automated or semi-automated step. For example, the assays can be set up using multiple-well plates in which cells are dispensed in individual wells and reagents are added in a systematic manner using a multiwell delivery device suited to the geometry of the multiwell plate. Manual and robotic multiwell delivery devices suitable for use in a high throughput screening assay are well known by those skilled in the art. Each well or array element can be mapped in a one-to-one manner to a particular test condition, such as the test compound. Readouts can also be performed in this multiwell array, preferably using a multiwell plate reader device or the like. Examples of such devices are well known in the art and are available through commercial sources. Sample and reagent handling can be automated to further enhance the throughput capacity of the screening assay, such that dozens, hundreds, thousands, or even millions of parallel assays can be performed in a day or in a week. Fully robotic systems are known in the art for applications such as generation and analysis of combinatorial libraries of synthetic compounds. See, for example, U.S. Pat. Nos. 5,443,791 and 5,708,158.

The following examples are provided for illustrative purposes and are not meant to be limiting in any way.

Examples

Example 1. Cloning and Sequencing of Rat, Porcine, Bovine, Equine, Ovine, Canine, and Feline TLR9

Cells and Tissues. Lymphoid tissues, primarily spleen or blood mononuclear cells (PBMC) from five mammalian species were collected: mouse, pig, bovine, rat and horse. Spleen samples were collected in RNA*later*™ (Ambion®, Austin, TX, USA), stabilized at 4°C overnight and stored at -70°C. Blood samples were centrifuged at 500 x g for 25 min at room temperature and the buffy coat, containing enriched PBMC, was then removed and stored at -70°C. The mouse specimen was used as a comparative positive control.

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First-strand cDNA synthesis. Total RNA from the spleen and PBMC samples was isolated using a monophasic solution of phenol and guanidine isothiocyanate: TRIzol™ reagent (GIBCO BRL®, Burlington, ON, Canada) according to the manufacturer's instructions. First-strand cDNA was synthesized from the total RNA using

5   SUPERSCRIPT™ II reverse transcriptase (GIBCO BRL®, Burlington, ON, Canada). Approximately 3 µg of total RNA was added to 50 pmoles of oligo(dT) primer [poly $T_{(18)}$]; the mixture was heated to 70°C for 10 min and subsequently chilled on ice. The following was added to the cooled reaction mixture: 1 µl of mixed dNTP stock containing 10 mM each dATP, dCTP, dGTP and dTTP (Amersham Pharmacia Biotech Inc., Baie de Urfe, Quebec) at

10   neutral pH, 1X first strand buffer (50 mM Tris-HCl pH 8.3/ 75 mM KCl/ 3 mM $MgCl_2$) and 2 µl of 0.1 M DTT. The mixture was subsequently heated to 42°C for 2 min, followed by addition of 200 units of SUPERSCRIPT™ II reverse transcriptase. The reaction was carried out at 42°C for 50 min, followed by 70°C for 15 min. The first-strand cDNA was used as the template for subsequent polymerase chain reaction (PCR) amplifications.

15   *PCR amplification.* TLR9 gene was PCR amplified from each of the above-mentioned species using primers designed from known mouse and human TLR9 sequence in Genbank: Accession AF314224 and AF259262, respectively. The primers were designed using the primer design software, Clone Manager 5 (Scientific and Educational Software, Durham, NC, USA). TLR9 gene-specific primers used were:

20   forward primer 5'-ACCTTGCCTGCCTTCCTACCCTGTGA-3' (SEQ ID NO:37) and reverse primer 5'-GTCCGTGTGGGCCAGCACAAA-3' (SEQ ID NO:38). The 2.7 Kbp fragment was PCR amplified using Advantage® 2 DNA polymerase mix (BD Biosciences Clontech, Palo Alto, CA, USA) according to the manufacturer's instructions. PCR reaction volumes of 25 µl contained 15 pmoles of each primer, 0.2 mM of dNTP mix

25   and 1 µl of reverse transcription reaction. PCR amplification was conducted by initial denaturation at 94°C for 1 min followed by 30 cycles of 94°C denaturation (15 sec), 65°C annealing (45 sec) and 72°C extensions (2 min), with a final extension at 72°C for 5 min.

         Cloning and sequencing. The PCR amplified fragment was treated with 500 units of T4 DNA polymerase (Amersham Pharmacia Biotech Inc., Baie de Urfe, Quebec) for 15 min

30   at room temperature prior to cleaning the reaction with QIAquick PCR purification kit (QIAGEN Inc., Mississauga, ON, Canada). The fragment was then ligated to pZErO™ - 2

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vector (Invitrogen™ Life Technologies, Burlington, ON, Canada), treated with *Eco RV*

restriction enzyme, using T4 DNA Ligase (GIBCO BRL®, Burlington, ON, Canada). *E. coli*

TOP 10 chemically competent cells (Invitrogen™ Life Technologies, Burlington, ON,

Canada) were used to transform ligated products. Plasmids containing the 2.7 Kbp fragment

5   were sequenced using an automated DNA sequencer, CEQ™ 2000XL DNA analysis system

(Beckman Coulter Inc., Fullerton, CA, USA).

Sequences of the 2.7 Kbp fragment were derived from three clones of each species

selected from independent PCR reactions to account for errors that may have been incurred

during the PCR amplifications and to confirm the sequence data.

10   Nucleotide sequences of the rat, porcine, bovine, equine, ovine, canine, and feline

TLR9 were extended and completed using standard 5' and 3' RACE PCR and primers

designed using the sequences obtained from the 2.7 Kbp fragments.

Results. Nucleotide sequences of rat, porcine, bovine, equine, canine, and feline

TLR9 cDNA obtained by the methods above are provided as SEQ ID NOs 3, 7, 11, 15, 19,

15   23, and 27, respectively. Deduced amino acid sequences are provided as SEQ ID NOs 1, 5,

9, 13, 17, 21, and 25, respectively. Deduced amino acid sequences of full-length murine and

human TLR9 are provided as SEQ ID NOs 29 and 33, respectively.

Example 2. Comparison of Aligned Sequences for TLR9 from Various Mammalian Species.

20   Multiple sequence alignment of deduced amino acid sequences for feline, canine,

bovine, mouse, ovine, porcine, horse, human, and rat TLR9 polypeptides was performed

using Clustal W 1.82 (see, for example, www.cmbi.kun.nl/bioinf/tools/clustalw.shtml). In

addition, paired sequence alignment of deduced amino acid sequences for murine and human

TLR9 polypeptides was performed using Clustal W 1.82. The results of the multiple

25   sequence alignment are presented in **Figure 1**. As will be appreciated from Figure 1, certain

amino acids are highly conserved across all species examined. Similarly, certain amino acids

differ only by conservative amino acid substitutions among the various species. In addition,

it is evident that certain amino acids which are conserved between murine and human TLR9

are not conserved in other species. Furthermore, Figure 1 also indicates that certain amino

30   acids are highly divergent across various species. The information provided by the

comparison of multiple species adds significantly to the information available by comparison

between only murine and human TLR9 sequences.

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The putative transmembrane regions of the TLR9 polypeptides are indicated in boxes in Figure 1. Sequence upstream of each transmembrane region is extracellular domain and is believed to include sequence primarily responsible for binding to TLR9 ligands, including CpG DNA. The extracellular domains of feline, canine, bovine, mouse, ovine, porcine,

5   horse, human, and rat TLR9 correspond to amino acids numbered 1-820, 1-822, 1-818, 1-821, 1-818, 1-819, 1-820, 1-820, and 1-821, respectively, as shown in Figure 1.

Figure 2 presents an evolutionary relatedness tree for six TLR9 polypeptides examined. The cladogram in Figure 2 was prepared using Clustal W (see above). As can be appreciated from this figure, murine and human TLR9 are nearly the most divergent TLR9s

10   in this group. Surprisingly, human and horse TLR9 appear relatively closely related.

Example 3. Reconstitution of TLR9 Signaling in 293 Fibroblasts.

Mouse TLR9 cDNA (SEQ ID NO:31) and human TLR9 cDNA (SEQ ID NO:35) in pT-Adv vector (from Clonetech) were individually cloned into the expression vector

15   pcDNA3.1(-) from Invitrogen using the EcoRI site. Utilizing a "gain of function" assay it was possible to reconstitute human TLR9 (hTLR9) and murine TLR9 (mTLR9) signaling in CpG-DNA non-responsive human 293 fibroblasts (ATCC, CRL-1573). The expression vectors mentioned above were transfected into 293 fibroblast cells using the calcium phosphate method.

20   Since NF-κB activation is central to the IL-1/TLR signal transduction pathway (Medzhitov R et al. (1998) *Mol Cell* 2:253-258; Muzio M et al. (1998) *J Exp Med* 187:2097-101), cells were transfected with hTLR9 or co-transfected with hTLR9 and an NF-κB-driven luciferase reporter construct. Human fibroblast 293 cells were transiently transfected with hTLR9 and a six-times NF-κB-luciferase reporter plasmid (NF-κB-luc) or with hTLR9 alone.

25   After stimulus with CpG-ODN (2006, 2μM, TCGTCGTTTTGTCGTTTTGTCGTT, SEQ ID NO:58), GpC-ODN (2006-GC, 2μM, TGCTGCTTTTGTGCTTTTGTGCTT, SEQ ID NO:59), LPS (100 ng/ml) or media, NF-κB activation by luciferase readout (8h) or IL-8 production by ELISA (48h) were monitored. Results representative of three independent experiments showed that cells expressing hTLR9 responded to CpG-DNA but not to LPS.

30   Independently, human fibroblast 293 cells were transiently transfected with mTLR9 and the NF-κB-luc construct or with mTLR9 alone. After stimulation with CpG-ODN (1668, 2μM; TCCATGACGTTCCTGATGCT, SEQ ID NO:60), GpC-ODN (1668-GC, 2μM;

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TCCATGAGCTTCCTGATGCT, SEQ ID NO:61), LPS (100 ng/ml) or media, NF-κB

activation by luciferase readout (8h) or IL-8 production by ELISA (48h) were monitored.

Results showed that expression of TLR9 (human or mouse) in 293 cells results in a gain of

function for CpG-DNA stimulation.

5   To generate stable clones expressing human TLR9, murine TLR9, or either TLR9

with the NF-κB-luc reporter plasmid, 293 cells were transfected in 10 cm plates (2x10^6

cells/plate) with 16 μg of DNA and selected with 0.7 mg/ml G418 (PAA Laboratories

GmbH, Cölbe, Germany). Clones were tested for TLR9 expression by RT-PCR. The clones

were also screened for IL-8 production or NF-κB-luciferase activity after stimulation with

10   ODN. Four different types of clones were generated.

293-hTLR9-luc: expressing human TLR9 and 6-fold NF-κB–luciferase reporter

293-mTLR9-luc: expressing murine TLR9 and 6-fold NF-κB–luciferase reporter

293-hTLR9:   expressing human TLR9

15   293-mTLR9:   expressing murine TLR9

Results indicated that stable clones also responded to CpG-ODN.

Example 4. Similar ODN Sequence Specificity of TLR9 of Human and Equine TLR9.

20   3x10^6 293T cells were electroporated with 5μg NF-κB-luc plasmid and 5 μg of either

horse TLR9-pcDNA3.1 plasmid or humanTLR9-pcDNA3.1 plasmid at 200V, 975 μF. After

the electroporation the cells were plated in 96-well cell culture plates at 2.5x10^4 cells per well

and grown overnight at 37°C. The cells were stimulated with the indicated concentration of

ODN for 16h, after which the supernatant was removed and the cells lysed in lysis buffer and

25   frozen for at least 2 hours at –80°C. Luciferase activity was measured by adding Luciferase

Assay substrate from Promega. Values are given as fold specific induction over non-

stimulated control. Results are shown in **Figure 3**.

          As shown in Figure 3, ODN 2006 (TCGTCGTTTTGTCGTTTTGTCGTT; SEQ ID

NO:58) has a strong specificity for human TLR9. ODN 1982

30   (TCCAGGACTTCTCTCAGGTT; SEQ ID NO:70) was the negative control ODN. ODN

5890 (TCCATGACGTTTTTGATGTT; SEQ ID NO:39) has a strong specificity for mouse

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TLR9. This experiment demonstrates the similarity of horse TLR9 to human TLR9 in binding specificity, a result predicted by the evolutionary relatedness of horse TLR9 to human TLR9. Mouse TLR9 is more distant from horse TLR9 and human TLR9 in sequence homology, and ODN 5890 was not detected by either human or horse TLR9.

Example 5. Non-human, Non-murine Native Mammalian TLR9 Useful in Screening for Human-Preferred CpG DNA.

Native rat, porcine, bovine, equine, and ovine TLR9 polypeptides are screened for binding or TLR9 signaling activity when contacted with human-preferred CpG DNA (ODN 2006). Rat, porcine, bovine, equine, or ovine TLR9 polypeptides which exhibit significant TLR9 binding or TLR9 signaling activity in this assay are then used as the basis for screening for additional human-preferred CpG DNA. An expression vector containing a nucleic acid sequence encoding a selected native rat, porcine, bovine, equine, or ovine TLR9 polypeptide, and optionally a reporter construct, is introduced into cells which do not express TLR9. The cells expressing the selected native rat, porcine, bovine, equine, or ovine TLR9 polypeptide are contacted with candidate human-preferred CpG DNA. Candidate human-preferred CpG DNA exhibiting significant TLR9 binding or TLR9 signaling activity are selected as human-preferred CpG DNA.

Example 6. Chimeric TLR9 Useful in Screening for Human-Preferred CpG DNA.

Chimeric TLR9 polypeptides are screened for binding or TLR9 signaling activity when contacted with human-preferred CpG DNA (ODN 2006). Chimeric TLR9 polypeptides which exhibit significant TLR9 binding or TLR9 signaling activity in this assay are then used as the basis for screening for additional human-preferred CpG DNA. An expression vector containing a nucleic acid sequence encoding a selected chimeric TLR9 polypeptide, and optionally a reporter construct, is introduced into cells which do not express TLR9. The cells expressing the selected chimeric TLR9 polypeptide are contacted with candidate human-preferred CpG DNA. Candidate human-preferred CpG DNA exhibiting significant TLR9 binding or TLR9 signaling activity are selected as human-preferred CpG DNA.

Example 7. Chimeric TLR9 Responsive to Both Human-Preferred and Murine-Preferred CpG DNA.

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Chimeric TLR9 polypeptides are screened for binding or TLR9 signaling activity when contacted with human-preferred CpG DNA (ODN 2006) and also screened for binding or TLR9 signaling activity when contacted with murine-preferred CpG DNA (ODN 1668). Chimeric TLR9 polypeptides which exhibit significant TLR9 binding or TLR9 signaling

5   activity in each of these assays are then used as the basis for screening for additional human-preferred CpG DNA and for screening for additional murine-preferred CpG DNA. An expression vector containing a nucleic acid sequence encoding a selected chimeric TLR9 polypeptide, and optionally a reporter construct, is introduced into cells which do not express TLR9. The cells expressing the selected chimeric TLR9 polypeptide are contacted with

10   candidate human-preferred CpG DNA or candidate murine-preferred CpG DNA. Candidate human-preferred CpG DNA exhibiting significant TLR9 binding or TLR9 signaling activity are selected as human-preferred CpG DNA. Candidate murine-preferred CpG DNA exhibiting significant TLR9 binding or TLR9 signaling activity are selected as murine-preferred CpG DNA.

15

Equivalents

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by examples provided, since the examples are intended as a single illustration of one aspect of

20   the invention and other functionally equivalent embodiments are within the scope of the invention. Various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims. The advantages of the invention are not necessarily encompassed by each embodiment of the invention.

25   All references, patents and patent publications that are recited in this application are incorporated in their entirety herein by reference.

We claim:

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Claims

1. An isolated polypeptide comprising an amino acid sequence selected from the group SEQ ID NO:1, SEQ ID NO:5, SEQ ID NO:9, SEQ ID NO:13, and SEQ ID NO:17.

2. An isolated polypeptide comprising an amino acid sequence selected from the group SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:10, SEQ ID NO:14, and SEQ ID NO:18.

3. An isolated nucleic acid molecule comprising a nucleic acid sequence encoding a polypeptide comprising an amino acid sequence selected from the group SEQ ID NO:1, SEQ ID NO:5, SEQ ID NO:9, SEQ ID NO:13, and SEQ ID NO:17.

4. An isolated nucleic acid molecule comprising a nucleic acid sequence encoding a polypeptide comprising an amino acid sequence selected from the group SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:10, SEQ ID NO:14, and SEQ ID NO:18.

5. A vector comprising the nucleic acid of any of claims 3-4.

6. A cell comprising the vector of claim 5.

7. An antibody or fragment thereof that binds specifically to the polypeptide of any of claims 1-2.

8. A method for identifying key amino acids in a TLR9 of a first species which confer specificity for CpG DNA optimized for TLR9 of the first species, comprising:
    aligning protein sequences of TLR9 of a first species, TLR9 of a second species, and TLR9 of a third species, wherein the TLR9 of the third species preferentially generates a signal when contacted with a CpG DNA optimized for TLR9 of the first species rather than when contacted with a CpG DNA optimized for TLR9 of the second species;
    generating an initial set of candidate amino acids in the TLR9 of the first species by excluding each amino acid in the TLR9 of the first species which (a) is identical with the

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TLR9 of the second species or (b) differs from the TLR9 of the second species only by conservative amino acid substitution;

generating a refined set of candidate amino acids by selecting each amino acid in the initial set of candidate amino acids in the TLR9 of the first species which (a) is identical with

5   the TLR9 of the third species or (b) differs from the TLR9 of the third species only by conservative amino acid substitution; and

identifying as key amino acids in the TLR9 of the first species each amino acid in the refined set of candidate amino acids.

10   9. A method for identifying key amino acids in human TLR9 which confer specificity for CpG DNA optimized for human TLR9, comprising:

aligning protein sequences of human TLR9, murine TLR9, and TLR9 of a third species, wherein the TLR9 of the third species preferentially generates a signal when contacted with a CpG DNA optimized for human TLR9 rather than when contacted with a

15   CpG DNA optimized for murine TLR9;

generating an initial set of candidate amino acids in human TLR9 by excluding each amino acid in human TLR9 which (a) is identical with murine TLR9 or (b) differs from
· murine TLR9 only by conservative amino acid substitution;

generating a refined set of candidate amino acids by selecting each amino acid in the

20   initial set of candidate amino acids in human TLR9 which (a) is identical with the TLR9 of the third species or (b) differs from the TLR9 of the third species only by conservative amino acid substitution; and

identifying as key amino acids in human TLR9 each amino acid in the refined set of candidate amino acids.

25

10. The method according to claim 9, performed iteratively with a plurality of TLR9s derived from different species other than human and mouse, wherein for each TLR9 the refined set of candidate amino acids is assigned a weight, said weight corresponding to a ratio equal to (responsiveness to human-preferred CpG DNA)/(responsiveness to murine-preferred

30   CpG DNA).

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11. An isolated polypeptide comprising an amino acid sequence identical to SEQ ID NO:30 except for substitution of at least one key amino acid identifed according to the method of any of claims 9 or 10.

12. An isolated nucleic acid molecule comprising a nucleic acid sequence encoding a polypeptide according to claim 11.

13. A vector comprising the nucleic acid of claim 12.

14. A cell comprising the vector of claim 13.

15. An antibody that binds specifically to the polypeptide of claim 14.

16. A screening method to identify a TLR9 ligand, comprising:

contacting a polypeptide according to any of claims 1, 2, or 11 with a candidate TLR9 ligand;

measuring a signal in response to the contacting; and

identifying the candidate TLR9 ligand as a TLR9 ligand when the signal in response to the contacting is consistent with TLR9 signaling.

17. The method of claim 16, wherein the signal comprises expression of a reporter gene responsive to TLR/IL-1R signal transduction pathway.

18. The method of claim 17, wherein the reporter gene is operatively linked to a promoter sensitive to NF-κB.

19. The method of claim 17, wherein the candidate TLR9 ligand is an immunostimulatory nucleic acid.

20. The method of claim 19, wherein the immunostimulatory nucleic acid is CpG DNA.

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21. A screening method to identify species-specific CpG-motif preference of an isolated polypeptide of claim 2 or claim 11, comprising:

contacting an isolated polypeptide of claim 2 or claim 11 with a CpG DNA comprising a hexamer sequence selected from the group consisting of GACGTT, AACGTT, CACGTT, TACGTT, GGCGTT, GCCGTT, GTCGTT, GATGTT, GAAGTT, GAGGTT, GACATT, GACCTT, GACTTT, GACGCT, GACGAT, GACGGT, GACGTC, GACGTA, and GACGTG;

measuring a signal in response to the contacting; and

identifying a species-specific CpG-motif preference when the signal in response to the contacting is consistent with TLR9 signaling.

22. The method of claim 21, wherein the signal comprises expression of a reporter gene responsive to TLR/IL-1R signal transduction pathway.

23. The method of claim 17, wherein the reporter gene is operatively linked to a promoter sensitive to NF-κB.

24. The method of claim 21, wherein the CpG DNA is an oligodeoxynucleotide having a sequence selected from the group consisting of

TCCATGACGTTTTTGATGTT	(SEQ ID NO:39),
TCCATAACGTTTTTGATGTT	(SEQ ID NO:40),
TCCATCACGTTTTTGATGTT	(SEQ ID NO:41),
TCCATTACGTTTTTGATGTT	(SEQ ID NO:42),
TCCATGGCGTTTTTGATGTT	(SEQ ID NO:43),
TCCATGCCGTTTTTGATGTT	(SEQ ID NO:44),
TCCATGTCGTTTTTGATGTT	(SEQ ID NO:45),
TCCATGATGTTTTTGATGTT	(SEQ ID NO:46),
TCCATGAAGTTTTTGATGTT	(SEQ ID NO:47),
TCCATGAGGTTTTTGATGTT	(SEQ ID NO:48),
TCCATGACATTTTTGATGTT	(SEQ ID NO:49),
TCCATGACCTTTTTGATGTT	(SEQ ID NO:50),
TCCATGACTTTTTTGATGTT	(SEQ ID NO:51),
TCCATGACGCTTTTGATGTT	(SEQ ID NO:52),
TCCATGACGATTTTGATGTT	(SEQ ID NO:53),
TCCATGACGGTTTTGATGTT	(SEQ ID NO:54),
TCCATGACGTCTTTGATGTT	(SEQ ID NO:55),
TCCATGACGTATTTGATGTT	(SEQ ID NO:56), and
TCCATGACGTGTTTGATGTT	(SEQ ID NO:57).

/

Figure 1
(1/3)

```
feline    MGPCHGALHPLSLLVQAAALAVALAQGTLPAFLPCELQRHGLVNCDWLFLKSVPHFSAAA 60
canine    MGPCRGALHPLSLLVQAAALALALAQGTLPAFLPCELQPHGLVNCNWLFLKSVPRFSAAA 60
bovine    MGP-YCAPHPLSLLVQAAALAAALAEGTLPAFLPCELQPHGQVDCNWLFLKSVPHFSAGA 59
mouse     MGP-YCAPHPLSLLVQAAALAAALAEGTLPAFLPCELQPHGQVDCNWLFLKSVPHFSAGA 59
ovine     MGP-YCAPHPLSLLVQAAALAAALAQGTLPAFLPCELQPRGKVNCNWLFLKSVPRFSAGA 59
porcine   MGP-RCTLHPLSLLVQVTALAAALAQGRLPAFLPCELQPHGLVNCNWLFLKSVPHFSAAA 59
horse     MGPCHGALQPLSLLVQAAMLAVALAQGTLPPFLPCELQPHGLVNCNWLFLKSVPHFSAAA 60
human     MGFCRSALHPLSLLVQAIMLAMTLALGTLPAFLPCELQPHGLVNCNWLFLKSVPHFSMAA 60
rat       MVLCRRTLHPLSLLVQAAVLAEALALGTLPAFLPCELKPHGLVDCNWLFLKSVPHFSAAE 60
          *     : :*******.   ** :** * **.******: :* *:*:*******:** .


feline    PRGNVTSLSLYSNRIHHLHDSDFVHLSSLRRLNLKWNCPPASLSPMHFPCHMTIEPHTFL 120
canine    PRGNVTSLSLYSNRIHHLHDYDFVHFVHLRRLNLKWNCPPASLSPMHFPCHMTIEPNTFL 120
bovine    PRANVTSLSLISNRIHHLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFL 119
mouse     PRANVTSLSLISNRIHHLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFL 119
ovine     PRANVTSLSLISNRIHHLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFL 119
porcine   PRANVTSLSLLSNRIHHLHDSDFVHLSSLRTLNLKWNCPPAGLSPMHFPCHMTIEPNTFL 119
horse     PRDNVTSLSLLSNRIHHLHDSDFAQLSNLQKLNLKWNCPPAGLSPMHFPCHMTIEPNTFL 120
human     PRGNVTSLSLSSNRIHHLHDSDFAHLPSLRHLNLKWNCPPVGLSPMHFPCHMTIEPSTFL 120
rat       PRSNITSLSLIANRIHHLHNLDFVHLPNVRQLNLKWNCPPPGLSPLHFSCRMTIEPKTFL 120
          ** *:***** :*******: **.::  :: ********* .***:**.*:***** ***


feline    AVPTLEELNLSYNSITTVPALPSSLVSLSLSRTNILVLDPANLAGLHSLRFLFLDGNCYY 180
canine    AVPTLEDLNLSYNSITTVPALPSSLVSLSLSRTNILVLDPATLAGLYALRFLFLDGNCYY 180
bovine    AVPTLEELNLSYNGITTVPALPSSLVSLSLSHTSILVLGPTHFTGLHALRFLYMDGNCYY 179
mouse     AVPTLEELNLSYNGITTVPALPSSLVSLSLSHTSILVLGPTHFTGLHALRFLYMDGNCYY 179
ovine     AVPTLEELNLSYNGITTVPALPSSLVSLSLSRTSILVLGPTHFTGLHALRFLYMDGNCYY 179
porcine   AVPTLEELNLSYNSITTVPALPDSLVSLSLSRTNILVLDPTHLTGLHALRYLYMDGNCYY 179
horse     AVPTLEELNLSYNGITTVPALPSSLVSLILSRTNILQLDPTSLTGLHALRFLYMDGNCYY 180
human     AVPTLEELNLSYNNIMTVPALPKSLISLSLSHTNILMLDSASLAGLHALRFLFMDGNCYY 180
rat       AMRMLEELNLSYNGITTVPRLPSSLTNLSLSHTNILVLDASSLAGLHSLRVLFMDGNCYY 180
          *:  **:****** * *** **.** .* **:*.** *..: ::**::** *::******


feline    KNPCPQALQVAPGALLGLGNLTHLSLKYNNLTAVPRGLPPSLEYLLLSYNHIITLAPEDL 240
canine    KNPCQQALQVAPGALLGLGNLTHLSLKYNNLTVVPRGLPPSLEYLLLSYNHIITLAPEDL 240
bovine    MNPCPRALEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLLLSYNHIVTLAPEDL 239
mouse     MNPCPRALEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLLLSYNHIVTLAPEDL 239
ovine     KNPCQQAVEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLLLSYNHIITLAPEDL 239
porcine   KNPCQGALEVVPGALLGLGNLTHLSLKYNNLTEVPRSLPPSLETLLLSYNHIVTLTPEDL 239
horse     KNPCGRALEVAPGALLGLGNLTHLSLKYNNLTTVPRSLPPSLEYLLLSYNHIVTLAPEDL 240
human     KNPCRQALEVAPGALLGLGNLTHLSLKYNNLTVVPRNLPSSLEYLLLSYNRIVKLAPEDL 240
rat       KNPCNGAVNVTPDAFLGLSNLTHLSLKYNNLTEVPRQLPPSLEYLLLSYNLIVKLGAEDL 240
          :***  *::*.*.*:*** ************ *** **.**: ****** *:.* .***


feline    ANLTALRVLDVGGNCRRCDHARNPCMECPKGFPHLHPDTFSHLNHLEGLVLKDSSLYNLN 300
canine    ANLTALRVLDVGGNCRRCDHARNPCRECPKGFPQLHPNTFGHLSHLEGLVLRDSSLYSLE 300
bovine    ANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLE 299
mouse     ANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLE 299
ovine     ANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLE 299
porcine   ANLTALRVLDVGGNCRRCDHARNPCRECPKDHPKLHSDTFSHLSRLEGLVLKDSSLYNLD 299
horse     ANLTALRVLDVGGNCRRCDHARNPCVECPHKFPQLHSDTFSHLSRLEGLVLKDSSLYQLN 300
human     ANLTALRVLDVGGNCRRCDHAPNPCMECPRHFPQLHPDTFSHLSRLEGLVLKDSSLSWLN 300
rat       ANLTSLRMLDVGGNCRRCDHAPDLCTECRQKSLDLHPQTFHHLSHLEGLVLKDSSLHSLN 300
          ****:**:************* : * ** :  .**.:** **.:******:****  *:


feline    PRWFHALGNLMVLDLSENFLYDCITKTTAFQGLAQLRRLNLSFNYHKKVSFAHLHLAPSF 360
canine    PRWFHGLGNLMVLDLSENFLYDCITKTKAFYGLARLRRLNLSFNYHKKVSFAHLHLASSF 360
bovine    KDWFRGLGRLQVLDLSENFLYDYITKTTIFNDLTQLRRLNLSFNYHKKVSFAHLHLASSF 359
mouse     KDWFRGLGRLQVLDLSENFLYDYITKTTIFNDLTQLRRLNLSFNYHKKVSFAHLHLASSF 359
ovine     KDWFRGLGRLQVLDLSENFLYDYITKTTIFRNLTQLRRLNLSFNYHKKVSFAHLQLAPSF 359
porcine   TRWFRGLDRLQVLDLSENFLYDCITKTTAFQGLARLRSLNLSFNYHKKVSFAHLHLAPSF 359
horse     PRWFRGLGNLTVLDLSENFLYDCITKTKAFQGLAQLRRLNLSFNYHKKVSFAHLTLAPSF 360
human     ASWFRGLGNLRVLDLSENFLYKCITKTKAFQGLTQLRKLNLSFNYQKRVSFAHLSLAPSF 360
rat       SKWFQGLANLSVLDLSENFLYESINKTSAFQNLTRLRKLDLSFNYCKKVSFARLHLASSF 360
          :**:.* .* *********.*.**. * .*::** *:***** *:****:* **.**
```

Figure 1
(2/3)

```
feline     GSLLSLQQLDMHGIFFRSLSETTLRSLVHLPMLQSLHLQMNFINQAQLSIFGAFPGLRYV 420
canine     GSLLSLQELDIHGIFFRSLSKTTLQSLAHLPMLQRLHLQLNFISQAQLSIFGAFPGLRYV 420
bovine     GSLVSLEKLDMHGIFFRSLTNITLQSLTRLPKLQSLHLQLNFINQAQLSIFGAFPSLLFV 419
mouse      GSLVSLEKLDMHGIFFRSLTNITLQSLTRLPKLQSLHLQLNFINQAQLSIFGAFPSLLFV 419
ovine      GGLVSLEKLDMHGIFFRSLTNTTLRPLTQLPKLQSLSLQLNFINQAELSIFGAFPSLLFV 419
porcine    GHLRSLKELDMHGIFFRSLSETTLQPLVQLPMLQTLRLQMNFINQAQLSIFGAFPGLLYV 419
horse      GSLLSLQELDMHGIFFRSLSQKTLQPLARLPMLQRLYLQMNFINQAQLGIFKDFPGLRYI 420
human      GSLVALKELDMHGIFFRSLDETTLRPLARLPMLQTLRLQMNFINQAQLGIFRAFPGLRYV 420
rat        KSLVSLQELNMNGIFFRLLNKNTLRWLAGLPKLHTLHLQMNFINQAQLSVFSTFRALRFV 420
                 * :*::*::*****  *  :  **: *. ** *: * **:***.**:*.:*  * .:* ::
```

```
feline     DLSDNRISGAMELAAATGEVDG--GERVRLPSGDLALGPPGTPSSEGFMPGCKTLNFTLD 478
canine     DLSDNRISGAAEPAAATGEVEADCGERVWPQSRDLALGPLGTPGSEAFMPSCRTLNFTLD 480
bovine     DLSDNRISGAATPAAALGEVDS--RVEVWRLPRGLAPGPLDAVSSKDFMPSCN-LNFTLD 476
mouse      DLSDNRISGAATPAAALGEVDS--RVEVWRLPRGLAPGPLDAVSSKDFMPSCN-LNFTLD 476
ovine      DLSDNRISGAARPVAALGEVDS--GVEVWRWPRGLAPGPLAAVSAKDFMPSCN-LNFTLD 476
porcine    DLSDNRISGAARPVAITREVDG--RERVWLPSRNLAPRPLDTLRSEDFMPNCKAFSFTLD 477
horse      DLSDNRISGAVEPVATTGEVDG--GKKVWLTSRDLTPGPLDTPSSEDFMPSCKNLSFTLD 478
human      DLSDNRISGASELTATMGEADG--GEKVWLQPGDLAPAPVDTPSSEDFRPNCSTLNFTLD 478
rat        DLSNNRISGPPTLSRVAPEKAD-EAEKGVPWPASLTPALPSTPVSKNFMVRCKNLRFTMD 479
           ***:*****.        *         . . .*:    :  :: *    *  : **:*
```

```
feline     LSRNNLVTIQPEMFARLSRLQCLLLSRNSISQAVNGSQFMPLTSLQVLDLSHNKLDLYHG 538
canine     LSRNNLVTVQPEMFVRLARLQCLGLSHNSISQAVNGSQFVPLSNLRVLDLSHNKLDLYHG 540
bovine     LSRNNLVTIQQEMFTRLSRLQCLRLSHNSISQAVNGSQFVPLTSLRVLDLSHNKLDLYHG 536
mouse      LSRNNLVTIQQEMFTRLSRLQCLRLSHNSISQAVNGSQFVPLTSLRVLDLSHNKLDLYHG 536
ovine      LSRNNLVTIQQEMFTRLSRLQCLRLSHNSISQAVNGSQFVPLTRLRVLDLSYNKLDLYHG 536
porcine    LSRNNLVTIQSEMFARLSRLECLRLSHNSISQAVNGSQFVPLTSLRVLDLSHNKLDLYHG 537
horse      LSRNNLVTVQPEMFAQLSRLQCLRLSHNSISQAVNGSQFVPLTSLQVLDLSHNKLDLYHG 538
human      LSRNNLVTVQPEMFAQLSHLQCLRLSHNCISQAVNGSQFLPLTGLQVLDLSHNKLDLYHE 538
rat        LSRNNQVTIKPEMFVNLSHLQCLSLSHNCIAQAVNGSQFLPLTNLKVLDLSYNKLDLYHS 539
           ***** **:: ***..*::*:** **:*.*:********:**: *:*****:*******
```

```
feline     RSFTELPRLEALDLSYNSQPFSMQGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCSA 598
canine     RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600
bovine     RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596
mouse      RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596
ovine      RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596
porcine    RSFTELPRLEALDLSYNSQPFTMQGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCSA 597
horse      RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598
human      HSFTELPRLEALDLSYNSQPFGMQGVGHNFSFVAHLRTLRHLSLAHNNIHSRVSSRLYST 598
rat        KSFSELPQLQALDLSYNSQPFSMQGIGHNFSFLANLSRLQNLSLAHNDIHSRVSSRLYST 599
           :**:***:*:********** *:*:***:**:*:*  *: ******.***:**.:* *:
```

```
feline     SLRALDFSGNALSRMWAEGDLYLHFFRGLRSLVRLDLSQNRLHTLLPRTLDNLPKSLRLL 658
canine     SLRALDFSGNTLSQMWAEGDLYLRFFQGLRSLVQLDLSQNRLHTLLPRNLDNLPKSLRLL 660
bovine     SLRALDFSGNSLSQMWAEGDLYLCFFKGLRNLVQLDLSENHLHTLLPRHLDNLPKSLRQL 656
mouse      SLRALDFSGNSLSQMWAEGDLYLCFFKGLRNLVQLDLSENHLHTLLPRHLDNLPKSLRQL 656
ovine      SLRALDFSGNSLSQMWAEGDLYLCFFKGLRNLVQLDLSKNHLHTLLPRHLDNLPKSLRQL 656
porcine    SLCALDFSGNDLSRMWAEGDLYLRFFQGLRSLVWLDLSQNHLHTLLPRALDNLPKSLKHL 657
horse      SLWALDFSGNSLSQMWAEGDLYLRFFQGLRSLIRLDLSQNRLHTLLPCTLGNLPKSLQLL 658
human      SLRALDFSGNALGHMWAEGDLYLHFFQGLSGLIWLDLSQNRLHTLLPQTLRNLPKSLQVL 658
rat        SVEYLDFSGNGVGRMWDEEDLYLYFFQDLRSLIHLDLSQNKLHILRPQNLNYLPKSLTKL 659
           *:  ****** :.:** * **** **:.* .*: ****:*:** * * *  ***** *
```

```
feline     RLRDNYLAFFNWSSLVLLPRLEALDLAGNQLKALSNGSLPNGTQLQRLDLSSNSISFVAS 718
canine     RLRDNYLAFFNWSSLALLPKLEALDLAGNQLKALSNGSLPNGTQLQRLDLSGNSIGFVVP 720
bovine     RLRDNNLAFFNWSSLTVLPRLEALDLAGNQLKALSNGSLPPGIRLQKLDVSSNSIGFVIP 716
mouse      RLRDNNLAFFNWSSLTVLPRLEALDLAGNQLKALSNGSLPPGIRLQKLDVSSNSIGFVIP 716
ovine      RLRDNNLAFFNWSSLTVLPQLEALDLAGNQLKALSNGSLPPGTRLQKLDVSSNSIGFVTP 716
porcine    HLRDNNLAFFNWSSLTLLPKLETLDLAGNQLKALSNGSLPSGTQLRRLDLSGNSIGFVNP 717
horse      RLRNNYLAFFNWSSLTLLPNLETLDLAGNQLKALSNGSLPSGTQLQRLDVSRNSIIFVVP 718
human      RLRDNYLAFFKWWSLHFLPKLEVLDLAGNQLKALTNGSLPAGTRLRRLDVSCNSISFVAP 718
rat        SFRDNHLSFFNWSSLAFLPNLRDLDLAGNLLKALTNGTLPNGTLLQKLDVSSNSIVFVVP 719
           .:*:* *:**:* ** .**.*. ***** ****:**:**  *  *::**:* *** ** .
```

Figure 1
(3/3)

```
feline    SFFALATRLRELNLSANALKTVEPSWFGSLAGTLKVLDVTGNPLHCACGAAFVDFLLEVQ 778
canine    SFFALAVRLRELNLSANALKTVEPSWFGSLAGALKVLDVTANPLHCACGATFVDFLLEVQ 780
bovine    GFFVRATRLIELNLSANALKTVDPSWFGSLAGTLKILDVSANPLHCACGAAFVDFLLERQ 776
mouse     GFFVRATRLIELNLSANALKTVDPSWFGSLAGTLKILDVSANPLHCACGAAFVDFLLERQ 776
ovine     GFFVLANRLKELNLSANALKTVDPFWFGRLTETLNILDVSANPLHCACGAAFVDFLLEMQ 776
porcine   GFFALAKQLEELNLSANALKTVEPSWFGSMVGNLKVLDVSANPLHCACGATFVGFLLEVQ 777
horse     GFFALATRLRELNLSANALRTEEPSWFGFLAGSLEVLDVSANPLHCACGAAFVDFLLQVQ 778
human     GFFSKAKELRELNLSANALKTVDHSWFGPLASALQILDVSANPLHCACGAAFMDFLLEVQ 778
rat       AFFALAVELKEVNLSHNILKTVDRSWFGPIVMNLTVLDVSSNPLHCACGAPFVDLLLEVQ 779
          .**  * .* :*** * *:*   :   *** :.   * :***:.********.*:.:**: *


feline    AAVPGLPGHVKCGSPGQLQGRSIFAQDLRLCLDEALSWDCFG⌐LSLLTVALGLAVPMLHHL⌐ 838
canine    AAVPGLPSRVKCGSPGQLQGRSIFAQDLRLCLDEALSWVCFS LSLLAVALSLAVPMLHQL  840
bovine    EAVPGLSRRVTCGSPGQLQGRSIFTQDLRLCLDETLSLDCFG LSLLMVALGLAVPMLHHI  836
mouse     EAVPGLSRRVTCGSPGQLQGRSIFTQDLRLCLDETLSLDCFG LSLLMVALGLAVPMLHHI  836
ovine     AAVPGLSRRVTCGSPGQLQGRSIFAQDLRLCLDETLSLDCFG FSLLMVALGLAVPMLHHI  836
porcine   AAVPGLPSRVKCGSPGQLQGHSIFAQDLRLCLDETLSWNCFG ISLLAMALGLVVPMLHHI  837
horse     AAVPGLPSRVKCGSPGQLQGRSIFAQDLRLCLDKSLSWDCFG LSLLVVALGLAMPMLHHI  838
human     AAVPGLPSRVKCGSPGQLQGLSIFAQDLRLCLDEALSWDCFA LSLLAVALGLGVPMLHHI  838
rat       TKVPGLANGVKCGSPRQLQGRSIFAQDLRLCLDDVLSRDCFG⌐LSLLAVAVGTVLPLLQHL⌐ 839
          ****.  *.**** **** ***:*******.  **  **.:*** :*:.   :*:*::*


feline    CGWDLWYCFHLCLAWLPRRGRR--RGADALPYDAFVVFDKAQSAVADWVYNELRVRLEER 896
canine    CGWDLWYCFHLCLAWLPRRGRR--RGVDALAYDAFVVFDKAQSSVADWVYNELRVQLEER 898
bovine    CGWDLWYCFHLCLAHLPRRRRQ--RGEDTLLYDAVVVFDKVQSAVADWVYNELRVQLEER 894
mouse     CGWDLWYCFHLCLAHLPRRRRQ--RGEDTLLYDAVVVFDKVQSAVADWVYNELRVQLEER 894
ovine     CGWDLWYCFHLCLAHLPRRRRQ--RGEDTLLYDAFVVFDKAQSAVADWVYNELRVQLEER 894
porcine   CGWDLWYCFHLCLAWLPHRGQR--RGADALFYDAFVVFDKAQSAVADWVYNELRVRLEER 895
horse     CGWDLWYCFHLCLAWLPRRGWQ--RGADALSYDAFVVFDKAQSAVADWVYNELRVRLEER 896
human     CGWDLWYCFHLCLAWLPWRGRQSGRDEDALPYDAFVVFDKTQSAVADWVYNELRGQLEEC 898
rat       CGWDVWYCFHLCLAWLPLLTGR-RSAQALPYDAFVVFDKAQSAVADWVYNELRVRLEER 898
          ****:****** ** **        *. ::* ***.*****.**:********** :***


feline    RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL 956
canine    RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL 958
bovine    RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL 954
mouse     RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL 954
ovine     RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL 954
porcine   RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL 955
horse     RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDQVSGLLRASFLLAQQRL 956
human     RGRWALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL 958
rat       RGRRALRLCLEDRDWLPGQTLFENLWASIYGSRKTLFVLAHTDKVSGLLRTSFLLAQQRL 958
          ***  *******:***:**:*********:*.*** :*** :**:****** :*********


feline    LEDRKDVVVLVILRPDAHRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGTALTRDNQ 1016
canine    LEDRKDVVVLVILCPDAHRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGTALTRDNR 1018
bovine    LEDRKDVVVLVILRPAAYRSRYVRLRQRLCRQSVLLWPHQPSGQGSFWANLGIALTRDNR 1014
mouse     LEDRKDVVVLVILRPAAYRSRYVRLRQRLCRQSVLLWPHQPSGQGSFWANLGIALTRDNR 1014
ovine     LEDRKDVVVLVILRPAAYRSRYVRLRQRLCRQSVLLWPHQPSGQGSFWANLGMALTRDNR 1014
porcine   LEDRKDVVVLVILRPDAYRSRYVRLRQRLCRQSVLLWPHQPRGQGSFWAQLGTALTRDNH 1015
horse     LEDRKDVVVLVILSPDARRSRYVRLRQRLCRQSVLFWPHQPSGQRSFWAQLGMALTRDNR 1016
human     LEDRKDVVVLVILSPDGRRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGSTALTRDNH 1018
rat       LEDRKDVVVLVILRPDAHRSRYVRLRQRLCRQSVLFWPHQPNGQGSFWAQLSTALTRDNH 1018
          ************ * .  *****************:***** ** ****:*.  *****:


feline    HFYNQNFCRGPTTAE------------------------------------------- 1031
canine    HFYNQNFCRGPTTA-------------------------------------------- 1032
bovine    HFYNRNFCRGPTTAE------------------------------------------- 1029
mouse     HFYNRNFCRGPTTAE------------------------------------------- 1032
ovine     HFYNRNFCRGPTTAE------------------------------------------- 1029
porcine   HFYNRNFCRGPTTAE------------------------------------------- 1030
horse     HFYNQNFCRGPTMAE------------------------------------------- 1031
human     HFYNRNFCQGPTAE-------------------------------------------- 1032
rat       HFYNRNFCRGPTAE-------------------------------------------- 1032
          ****:***:***
```

Figure 2
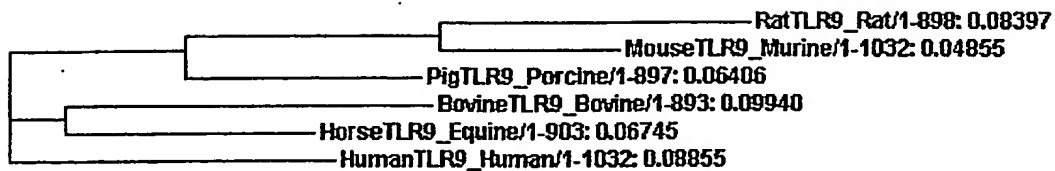
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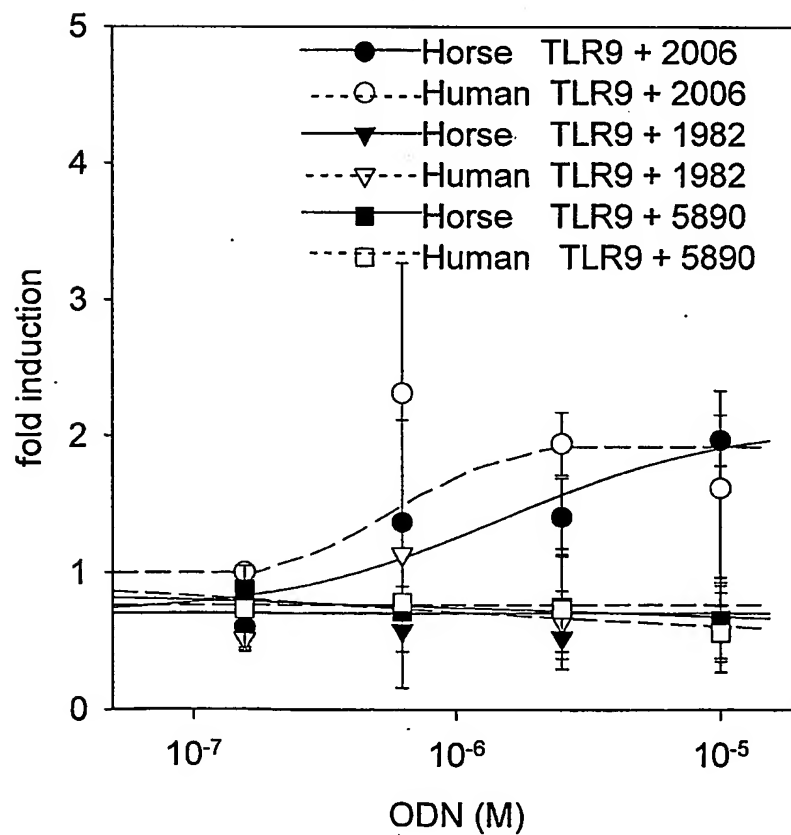
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       University of Saskatchewan
       Qiagen GmbH

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<130> C1041.70040WO00

<150> US 60/412,479
<151> 2002-09-19

<160> 70

<170> PatentIn version 3.1

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1   5   10   15

Ala Ala Val Leu Ala Glu Ala Leu Ala Leu Gly Thr Leu Pro Ala Phe
                20   25   30

Leu Pro Cys Glu Leu Lys Pro His Gly Leu Val Asp Cys Asn Trp Leu
            35   40   45

Phe Leu Lys Ser Val Pro His Phe Ser Ala Ala Glu Pro Arg Ser Asn
    50   55   60

Ile Thr Ser Leu Ser Leu Ile Ala Asn Arg Ile His His Leu His Asn
65   70   75   80

Leu Asp Phe Val His Leu Pro Asn Val Arg Gln Leu Asn Leu Lys Trp
                85   90   95

Asn Cys Pro Pro Pro Gly Leu Ser Pro Leu His Phe Ser Cys Arg Met
            100   105   110

Thr Ile Glu Pro Lys Thr Phe Leu Ala Met Arg Met Leu Glu Glu Leu
            115   120   125

Asn Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Arg Leu Pro Ser Ser
    130   135   140

```
Leu Thr Asn Leu Ser Leu Ser His Thr Asn Ile Leu Val Leu Asp Ala
145                 150             155                 160


Ser Ser Leu Ala Gly Leu His Ser Leu Arg Val Leu Phe Met Asp Gly
                165             170                 175


Asn Cys Tyr Tyr Lys Asn Pro Cys Asn Gly Ala Val Asn Val Thr Pro
            180             185                 190


Asp Ala Phe Leu Gly Leu Ser Asn Leu Thr His Leu Ser Leu Lys Tyr
        195             200             205


Asn Asn Leu Thr Glu Val Pro Arg Gln Leu Pro Pro Ser Leu Glu Tyr
    210             215             220


Leu Leu Leu Ser Tyr Asn Leu Ile Val Lys Leu Gly Ala Glu Asp Leu
225             230             235                 240


Ala Asn Leu Thr Ser Leu Arg Met Leu Asp Val Gly Gly Asn Cys Arg
            245             250                 255


Arg Cys Asp His Ala Pro Asp Leu Cys Thr Glu Cys Arg Gln Lys Ser
            260             265             270


Leu Asp Leu His Pro Gln Thr Phe His His Leu Ser His Leu Glu Gly
        275             280             285


Leu Val Leu Lys Asp Ser Ser Leu His Ser Leu Asn Ser Lys Trp Phe
    290             295             300


Gln Gly Leu Ala Asn Leu Ser Val Leu Asp Leu Ser Glu Asn Phe Leu
305             310             315                 320


Tyr Glu Ser Ile Asn Lys Thr Ser Ala Phe Gln Asn Leu Thr Arg Leu
            325             330             335


Arg Lys Leu Asp Leu Ser Phe Asn Tyr Cys Lys Lys Val Ser Phe Ala
            340             345             350


Arg Leu His Leu Ala Ser Ser Phe Lys Ser Leu Val Ser Leu Gln Glu
        355             360             365


Leu Asn Met Asn Gly Ile Phe Phe Arg Leu Leu Asn Lys Asn Thr Leu
    370             375             380
```

-2-

```
Arg Trp Leu Ala Gly Leu Pro Lys Leu His Thr Leu His Leu Gln Met
385             390             395                     400

Asn Phe Ile Asn Gln Ala Gln Leu Ser Val Phe Ser Thr Phe Arg Ala
            405             410                 415

Leu Arg Phe Val Asp Leu Ser Asn Asn Arg Ile Ser Gly Pro Pro Thr
        420             425             430

Leu Ser Arg Val Ala Pro Glu Lys Ala Asp Glu Ala Glu Lys Gly Val
        435             440             445

Pro Trp Pro Ala Ser Leu Thr Pro Ala Leu Pro Ser Thr Pro Val Ser
    450             455             460

Lys Asn Phe Met Val Arg Cys Lys Asn Leu Arg Phe Thr Met Asp Leu
465             470             475                     480

Ser Arg Asn Asn Gln Val Thr Ile Lys Pro Glu Met Phe Val Asn Leu
            485             490                 495

Ser His Leu Gln Cys Leu Ser Leu Ser His Asn Cys Ile Ala Gln Ala
        500             505             510

Val Asn Gly Ser Gln Phe Leu Pro Leu Thr Asn Leu Lys Val Leu Asp
        515             520             525

Leu Ser Tyr Asn Lys Leu Asp Leu Tyr His Ser Lys Ser Phe Ser Glu
        530             535             540

Leu Pro Gln Leu Gln Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe
545             550             555                     560

Ser Met Gln Gly Ile Gly His Asn Phe Ser Phe Leu Ala Asn Leu Ser
            565             570                 575

Arg Leu Gln Asn Leu Ser Leu Ala His Asn Asp Ile His Ser Arg Val
            580             585                 590

Ser Ser Arg Leu Tyr Ser Thr Ser Val Glu Tyr Leu Asp Phe Ser Gly
        595             600             605

Asn Gly Val Gly Arg Met Trp Asp Glu Glu Asp Leu Tyr Leu Tyr Phe
```

-3-

```
            610                    615                    620


Phe Gln Asp Leu Arg Ser Leu Ile His Leu Asp Leu Ser Gln Asn Lys
625             630              635              640


Leu His Ile Leu Arg Pro Gln Asn Leu Asn Tyr Leu Pro Lys Ser Leu
                645              650              655


Thr Lys Leu Ser Phe Arg Asp Asn His Leu Ser Phe Phe Asn Trp Ser
            660              665              670


Ser Leu Ala Phe Leu Pro Asn Leu Arg Asp Leu Asp Leu Ala Gly Asn
        675              680              685


Leu Leu Lys Ala Leu Thr Asn Gly Thr Leu Pro Asn Gly Thr Leu Leu
    690              695              700


Gln Lys Leu Asp Val Ser Ser Asn Ser Ile Val Phe Val Val Pro Ala
705             710              715              720


Phe Phe Ala Leu Ala Val Glu Leu Lys Glu Val Asn Leu Ser His Asn
            725              730              735


Ile Leu Lys Thr Val Asp Arg Ser Trp Phe Gly Pro Ile Val Met Asn
            740              745              750


Leu Thr Val Leu Asp Val Ser Ser Asn Pro Leu His Cys Ala Cys Gly
    755              760              765


Ala Pro Phe Val Asp Leu Leu Leu Glu Val Gln Thr Lys Val Pro Gly
    770              775              780


Leu Ala Asn Gly Val Lys Cys Gly Ser Pro Arg Gln Leu Gln Gly Arg
785             790              795              800


Ser Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Asp Val Leu Ser
            805              810              815


Arg Asp Cys Phe Gly Leu Ser Leu Leu Ala Val Ala Val Gly Thr Val
            820              825              830


Leu Pro Leu Leu Gln His Leu Cys Gly Trp Asp Val Trp Tyr Cys Phe
        835              840              845
```

His Leu Cys Leu Ala Trp Leu Pro Leu Leu Thr Arg Gly Arg Arg Ser
    850   855   860

Ala Gln Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Ala Gln
865   870   875   880

Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Val Arg Leu Glu
                885   890   895

Glu Arg Arg Gly Arg Arg Ala Leu Arg Leu Cys Leu Glu Asp Arg Asp
            900   905   910

Trp Leu Pro Gly Gln Thr Leu Phe Glu Asn Leu Trp Ala Ser Ile Tyr
        915   920   925

Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Lys Val Ser
    930   935   940

Gly Leu Leu Arg Thr Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu
945   950   955   960

Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Arg Pro Asp Ala His
            965   970   975

Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val
            980   985   990

Leu Phe Trp Pro His Gln Pro Asn Gly Gln Gly Ser Phe Trp Ala Gln
        995   1000   1005

Leu Ser Thr Ala Leu Thr Arg Asp Asn His His Phe Tyr Asn Arg
    1010   1015   1020

Asn Phe Cys Arg Gly Pro Thr Ala Glu
    1025   1030

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<212>   PRT
<213>   Rattus norvegicus

<400>   2

Met Val Leu Cys Arg Arg Thr Leu His Pro Leu Ser Leu Leu Val Gln
1   5   10   15

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Ala Ala Val Leu Ala Glu Ala Leu Ala Leu Gly Thr Leu Pro Ala Phe
            20              25              30

Leu Pro Cys Glu Leu Lys Pro His Gly Leu Val Asp Cys Asn Trp Leu
            35              40              45

Phe Leu Lys Ser Val Pro His Phe Ser Ala Ala Glu Pro Arg Ser Asn
            50              55              60

Ile Thr Ser Leu Ser Leu Ile Ala Asn Arg Ile His His Leu His Asn
65              70              75              80

Leu Asp Phe Val His Leu Pro Asn Val Arg Gln Leu Asn Leu Lys Trp
                85              90              95

Asn Cys Pro Pro Pro Gly Leu Ser Pro Leu His Phe Ser Cys Arg Met
            100             105             110

Thr Ile Glu Pro Lys Thr Phe Leu Ala Met Arg Met Leu Glu Glu Leu
            115             120             125

Asn Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Arg Leu Pro Ser Ser
            130             135             140

Leu Thr Asn Leu Ser Leu Ser His Thr Asn Ile Leu Val Leu Asp Ala
145             150             155             160

Ser Ser Leu Ala Gly Leu His Ser Leu Arg Val Leu Phe Met Asp Gly
                165             170             175

Asn Cys Tyr Tyr Lys Asn Pro Cys Asn Gly Ala Val Asn Val Thr Pro
            180             185             190

Asp Ala Phe Leu Gly Leu Ser Asn Leu Thr His Leu Ser Leu Lys Tyr
            195             200             205

Asn Asn Leu Thr Glu Val Pro Arg Gln Leu Pro Pro Ser Leu Glu Tyr
            210             215             220

Leu Leu Leu Ser Tyr Asn Leu Ile Val Lys Leu Gly Ala Glu Asp Leu
225             230             235             240

Ala Asn Leu Thr Ser Leu Arg Met Leu Asp Val Gly Gly Asn Cys Arg
            245             250             255
```

```
Arg Cys Asp His Ala Pro Asp Leu Cys Thr Glu Cys Arg Gln Lys Ser
            260              265              270

Leu Asp Leu His Pro Gln Thr Phe His His Leu Ser His Leu Glu Gly
        275              280              285

Leu Val Leu Lys Asp Ser Ser Leu His Ser Leu Asn Ser Lys Trp Phe
        290              295              300

Gln Gly Leu Ala Asn Leu Ser Val Leu Asp Leu Ser Glu Asn Phe Leu
305              310              315              320

Tyr Glu Ser Ile Asn Lys Thr Ser Ala Phe Gln Asn Leu Thr Arg Leu
                325              330              335

Arg Lys Leu Asp Leu Ser Phe Asn Tyr Cys Lys Lys Val Ser Phe Ala
            340              345              350

Arg Leu His Leu Ala Ser Ser Phe Lys Ser Leu Val Ser Leu Gln Glu
        355              360              365

Leu Asn Met Asn Gly Ile Phe Phe Arg Leu Leu Asn Lys Asn Thr Leu
    370              375              380

Arg Trp Leu Ala Gly Leu Pro Lys Leu His Thr Leu His Leu Gln Met
385              390              395              400

Asn Phe Ile Asn Gln Ala Gln Leu Ser Val Phe Ser Thr Phe Arg Ala
            405              410              415

Leu Arg Phe Val Asp Leu Ser Asn Asn Arg Ile Ser Gly Pro Pro Thr
        420              425              430

Leu Ser Arg Val Ala Pro Glu Lys Ala Asp Glu Ala Glu Lys Gly Val
    435              440              445

Pro Trp Pro Ala Ser Leu Thr Pro Ala Leu Pro Ser Thr Pro Val Ser
    450              455              460

Lys Asn Phe Met Val Arg Cys Lys Asn Leu Arg Phe Thr Met Asp Leu
465              470              475              480

Ser Arg Asn Asn Gln Val Thr Ile Lys Pro Glu Met Phe Val Asn Leu
            485              490              495
```

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Ser His Leu Gln Cys Leu Ser Leu Ser His Asn Cys Ile Ala Gln Ala
            500   505   510

Val Asn Gly Ser Gln Phe Leu Pro Leu Thr Asn Leu Lys Val Leu Asp
            515   520   525

Leu Ser Tyr Asn Lys Leu Asp Leu Tyr His Ser Lys Ser Phe Ser Glu
            530   535   540

Leu Pro Gln Leu Gln Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe
545   550   555   560

Ser Met Gln Gly Ile Gly His Asn Phe Ser Phe Leu Ala Asn Leu Ser
                565   570   575

Arg Leu Gln Asn Leu Ser Leu Ala His Asn Asp Ile His Ser Arg Val
            580   585   590

Ser Ser Arg Leu Tyr Ser Thr Ser Val Glu Tyr Leu Asp Phe Ser Gly
            595   600   605

Asn Gly Val Gly Arg Met Trp Asp Glu Glu Asp Leu Tyr Leu Tyr Phe
        610   615   620

Phe Gln Asp Leu Arg Ser Leu Ile His Leu Asp Leu Ser Gln Asn Lys
625   630   635   -   -   640

Leu His Ile Leu Arg Pro Gln Asn Leu Asn Tyr Leu Pro Lys Ser Leu
                645   650   655

Thr Lys Leu Ser Phe Arg Asp Asn His Leu Ser Phe Phe Asn Trp Ser
            660   665   670

Ser Leu Ala Phe Leu Pro Asn Leu Arg Asp Leu Asp Leu Ala Gly Asn
            675   680   685

Leu Leu Lys Ala Leu Thr Asn Gly Thr Leu Pro Asn Gly Thr Leu Leu
            690   695   700

Gln Lys Leu Asp Val Ser Ser Asn Ser Ile Val Phe Val Val Pro Ala
705   710   715   720

Phe Phe Ala Leu Ala Val Glu Leu Lys Glu Val Asn Leu Ser His Asn

```
                725                      730                      735
```

Ile Leu Lys Thr Val Asp Arg Ser Trp Phe Gly Pro Ile Val Met Asn
          740   745   750

Leu Thr Val Leu Asp Val Ser Ser Asn Pro Leu His Cys Ala Cys Gly
          755   760   765

Ala Pro Phe Val Asp Leu Leu Leu Glu Val Gln Thr Lys Val Pro Gly
    770   775   780

Leu Ala Asn Gly Val Lys Cys Gly Ser Pro Arg Gln Leu Gln Gly Arg
785   790   795   800

Ser Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Asp Val Leu Ser
              805   810   815

Arg Asp Cys Phe Gly
          820

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<212>   DNA
<213>   Rattus norvegicus

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ggcctggtag actgcaactg gctcttcctg aagtctgtgc tcacttctc tgccgcagaa   180

ccccgttcca acatcaccag cctttccttg atcgccaacc gcatccacca cctgcacaac   240

ctcgactttg tccacctgcc caacgtgcga cagctgaacc tcaagtggaa ctgtccgccc   300   !

cctggcctca gccccttgca cttctcctgc cgcatgacca ttgagcccaa aaccttcctg   360

gctatgcgca tgctggaaga gctgaacctg agctataacg tatcaccac tgtgccccgc   420

ctgcccagct ccctgacgaa tctgagccta agccacacca acatcctggt actcgatgcc   480

agcagcctcg ctggcctgca gcctgcga gttctcttca tggacgggaa ctgctactac   540

aagaacccct gcaacggggc ggtgaacgtg accccggacg ccttcctggg cttgagcaac   600

ctcacccact tgtcccttaa gtataacaac ctcacagagg tgccccgcca actgccccc   660

agcctggagt acctcctgct gtcctataac ctcatcgtca agctggggc cgaagaccta   720

gccaacctga cctcccttcg aatgcttgat gtgggtggga attgccgtcg ctgtgatcac   780
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tacgagagca tcaacaaaac cagcgccttt cagaacctga cccgtctgcg caagctcgac    1020

ctgtccttca attactgcaa gaaggtatcg ttcgcccgcc tccacctggc aagttccttc    1080

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cgccgagccc tacgcttgtg tctggaggac cgagattggc tgcctggcca gacactcttc    2760

gagaacctct gggcctccat ctatggcagc cgcaagactc tgtttgtgct ggcccacacg    2820

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gtgcgactgc gccagcgcct ctgccgccag agtgtgctct tctggcccca tcagcccaac    3000

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<212>   DNA
<213>   Rattus norvegicus

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<212>  PRT
<213>  Sus scrofa

<400>  5
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Thr Ala Leu Ala Ala Ala Leu Ala Gln Gly Arg Leu Pro Ala Phe Leu
            20              25                  30


Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu Phe
        35              40                  45


Leu Lys Ser Val Pro His Phe Ser Ala Ala Ala Pro Arg Ala Asn Val
        50              55                  60


Thr Ser Leu Ser Leu Leu Ser Asn Arg Ile His His Leu His Asp Ser
65              70                  75                  80


Asp Phe Val His Leu Ser Ser Leu Arg Thr Leu Asn Leu Lys Trp Asn
            85                  90                  95


Cys Pro Pro Ala Gly Leu Ser Pro Met His Phe Pro Cys His Met Thr
            100             105                 110


Ile Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu Asn
            115             120                 125


Leu Ser Tyr Asn Ser Ile Thr Thr Val Pro Ala Leu Pro Asp Ser Leu
    130             135                 140


Val Ser Leu Ser Leu Ser Arg Thr Asn Ile Leu Val Leu Asp Pro Thr
145                 150             155                 160


His Leu Thr Gly Leu His Ala Leu Arg Tyr Leu Tyr Met Asp Gly Asn
                165             170                 175


Cys Tyr Tyr Lys Asn Pro Cys Gln Gly Ala Leu Glu Val Val Pro Gly
            180             185                 190


Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr Asn
        195             200             205


Asn Leu Thr Glu Val Pro Arg Ser Leu Pro Pro Ser Leu Glu Thr Leu
    210             215             220


Leu Leu Ser Tyr Asn His Ile Val Thr Leu Thr Pro Glu Asp Leu Ala
225             230             235             240
```

Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg Arg
              245   250   255

Cys Asp His Ala Arg Asn Pro Cys Arg Glu Cys Pro Lys Asp His Pro
              260   265   270

Lys Leu His Ser Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly Leu
              275   280   285

Val Leu Lys Asp Ser Ser Leu Tyr Asn Leu Asp Thr Arg Trp Phe Arg
      290   295   300

Gly Leu Asp Arg Leu Gln Val Leu Asp Leu Ser Glu Asn Phe Leu Tyr
305   310   315   320

Asp Cys Ile Thr Lys Thr Thr Ala Phe Gln Gly Leu Ala Arg Leu Arg
              325   330   335

Ser Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala His
              340   345   350

Leu His Leu Ala Pro Ser Phe Gly His Leu Arg Ser Leu Lys Glu Leu
              355   360   365

Asp Met His Gly Ile Phe Phe Arg Ser Leu Ser Glu Thr Thr Leu Gln
      370   375   380

Pro Leu Val Gln Leu Pro Met Leu Gln Thr Leu Arg Leu Gln Met Asn
385   390   395   400

Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Ala Phe Pro Gly Leu
              405   410   415

Leu Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ala Arg Pro
              420   425   430

Val Ala Ile Thr Arg Glu Val Asp Gly Arg Glu Arg Val Trp Leu Pro
              435   440   445

Ser Arg Asn Leu Ala Pro Arg Pro Leu Asp Thr Leu Arg Ser Glu Asp
      450   455   460

Phe Met Pro Asn Cys Lys Ala Phe Ser Phe Thr Leu Asp Leu Ser Arg
465   470   475   480

Asn Asn Leu Val Thr Ile Gln Ser Glu Met Phe Ala Arg Leu Ser Arg
                485   490   495

Leu Glu Cys Leu Arg Leu Ser His Asn Ser Ile Ser Gln Ala Val Asn
            500   505   510

Gly Ser Gln Phe Val Pro Leu Thr Ser Leu Arg Val Leu Asp Leu Ser
            515   520   525

His Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr Glu Leu Pro
    530   535   540

Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Thr Met
545   550   555   560

Gln Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu Pro Ala Leu
            565   570   575

Arg Tyr Leu Ser Leu Ala His Asn Asp Ile His Ser Arg Val Ser Gln
            580   585   590

Gln Leu Cys Ser Ala Ser Leu Cys Ala Leu Asp Phe Ser Gly Asn Asp
    595   600   605

Leu Ser Arg Met Trp Ala Glu Gly Asp Leu Tyr Leu Arg Phe Phe Gln
610   615   620

Gly Leu Arg Ser Leu Val Trp Leu Asp Leu Ser Gln Asn His Leu His
625   630   635   640

Thr Leu Leu Pro Arg Ala Leu Asp Asn Leu Pro Lys Ser Leu Lys His
            645   650   655

Leu His Leu Arg Asp Asn Asn Leu Ala Phe Phe Asn Trp Ser Ser Leu
            660   665   670

Thr Leu Leu Pro Lys Leu Glu Thr Leu Asp Leu Ala Gly Asn Gln Leu
    675   680   685

Lys Ala Leu Ser Asn Gly Ser Leu Pro Ser Gly Thr Gln Leu Arg Arg
    690   695   700

Leu Asp Leu Ser Gly Asn Ser Ile Gly Phe Val Asn Pro Gly Phe Phe

```
705                    710                  715                  720
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Ala Leu Ala Lys Gln Leu Glu Glu Leu Asn Leu Ser Ala Asn Ala Leu
            725   730   735

Lys Thr Val Glu Pro Ser Trp Phe Gly Ser Met Val Gly Asn Leu Lys
            740   745   750

Val Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala Thr
            755   760   765

Phe Val Gly Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu Pro
            770   775   780

Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly His Ser Ile
785   790   795   800

Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Thr Leu Ser Trp Asn
                805   810   815

Cys Phe Gly Ile Ser Leu Leu Ala Met Ala Leu Gly Leu Val Val Pro
                820   825   830

Met Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His Leu
            835   840   845

Cys Leu Ala Trp Leu Pro His Arg Gly Gln Arg Arg Gly Ala Asp Ala
            850   855   860

Leu Phe Tyr Asp Ala Phe Val Val Phe Asp Lys Ala Gln Ser Ala Val
865   870   875   880

Ala Asp Trp Val Tyr Asn Glu Leu Arg Val Gln Leu Glu Glu Arg Arg
                885   890   895

Gly Arg Arg Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp Trp Leu Pro
            900   905   910

Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr Ser Ser Arg
            915   920   925

Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser Gly Leu Leu
            930   935   940

Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu Asp Arg Lys
945   950.   955   960

Asp Val Val Val Leu Val Ile Leu Arg Pro Asp Ala Tyr Arg Ser Arg
                965   970   975

Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val Leu Leu Trp
            980   985   990

Pro His Gln Pro Arg Gly Gln Gly Ser Phe Trp Ala Gln Leu Gly Thr
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Ala Leu Thr Arg Asp Asn His His Phe Tyr Asn Arg Asn Phe Cys
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Arg Gly Pro Thr Thr Ala Glu
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<213> Sus scrofa

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Thr Ala Leu Ala Ala Ala Leu Ala Gln Gly Arg Leu Pro Ala Phe Leu
            20   25   30

Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu Phe
            35   40   45

Leu Lys Ser Val Pro His Phe Ser Ala Ala Ala Pro Arg Ala Asn Val
    50   55   60

Thr Ser Leu Ser Leu Leu Ser Asn Arg Ile His His Leu His Asp Ser
65   70   75   80

Asp Phe Val His Leu Ser Ser Leu Arg Thr Leu Asn Leu Lys Trp Asn
            85   90   95

Cys Pro Pro Ala Gly Leu Ser Pro Met His Phe Pro Cys His Met Thr
            100   105   110

Ile Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu Asn
        115   120   125

Leu Ser Tyr Asn Ser Ile Thr Thr Val Pro Ala Leu Pro Asp Ser Leu
        130   135   140

Val Ser Leu Ser Leu Ser Arg Thr Asn Ile Leu Val Leu Asp Pro Thr
145   150   155   160

His Leu Thr Gly Leu His Ala Leu Arg Tyr Leu Tyr Met Asp Gly Asn
                165   170   175

Cys Tyr Tyr Lys Asn Pro Cys Gln Gly Ala Leu Glu Val Val Pro Gly
            180   185   190

Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr Asn
        195   200   205

Asn Leu Thr Glu Val Pro Arg Ser Leu Pro Pro Ser Leu Glu Thr Leu
        210   215   220

Leu Leu Ser Tyr Asn His Ile Val Thr Leu Thr Pro Glu Asp Leu Ala
225   230   235   240

Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg Arg
                245   250   255

Cys Asp His Ala Arg Asn Pro Cys Arg Glu Cys Pro Lys Asp His Pro
            260   265   270

Lys Leu His Ser Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly Leu
        275   280   285

Val Leu Lys Asp Ser Ser Leu Tyr Asn Leu Asp Thr Arg Trp Phe Arg
        290   295   300

Gly Leu Asp Arg Leu Gln Val Leu Asp Leu Ser Glu Asn Phe Leu Tyr
305   310   315   320

Asp Cys Ile Thr Lys Thr Thr Ala Phe Gln Gly Leu Ala Arg Leu Arg
            325   330   335

Ser Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala His
        340   345   350

Leu His Leu Ala Pro Ser Phe Gly His Leu Arg Ser Leu Lys Glu Leu
        355   360   365

Asp Met His Gly Ile Phe Phe Arg Ser Leu Ser Glu Thr Thr Leu Gln
        370   375   380

Pro Leu Val Gln Leu Pro Met Leu Gln Thr Leu Arg Leu Gln Met Asn
385   390   395   400

Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Ala Phe Pro Gly Leu
                405   410   415

Leu Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ala Arg Pro
            420   425   430

Val Ala Ile Thr Arg Glu Val Asp Gly Arg Glu Arg Val Trp Leu Pro
        435   440   445

Ser Arg Asn Leu Ala Pro Arg Pro Leu Asp Thr Leu Arg Ser Glu Asp
    450   455   460

Phe Met Pro Asn Cys Lys Ala Phe Ser Phe Thr Leu Asp Leu Ser Arg
465   470   475   480

Asn Asn Leu Val Thr Ile Gln Ser Glu Met Phe Ala Arg Leu Ser Arg
                485   490   495

Leu Glu Cys Leu Arg Leu Ser His Asn Ser Ile Ser Gln Ala Val Asn
            500   505   510

Gly Ser Gln Phe Val Pro Leu Thr Ser Leu Arg Val Leu Asp Leu Ser
        515   520   525

His Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr Glu Leu Pro
        530   535   540

Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Thr Met
545   550   555   560

Gln Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu Pro Ala Leu
            565   570   575

Arg Tyr Leu Ser Leu Ala His Asn Asp Ile His Ser Arg Val Ser Gln
        580   585   590

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Gln Leu Cys Ser Ala Ser Leu Cys Ala Leu Asp Phe Ser Gly Asn Asp
        595   600   605

Leu Ser Arg Met Trp Ala Glu Gly Asp Leu Tyr Leu Arg Phe Phe Gln
    610   615   620

Gly Leu Arg Ser Leu Val Trp Leu Asp Leu Ser Gln Asn His Leu His
625   630   635   640

Thr Leu Leu Pro Arg Ala Leu Asp Asn Leu Pro Lys Ser Leu Lys His
                645   650   655

Leu His Leu Arg Asp Asn Asn Leu Ala Phe Phe Asn Trp Ser Ser Leu
                660   665   670

Thr Leu Leu Pro Lys Leu Glu Thr Leu Asp Leu Ala Gly Asn Gln Leu
        675   680   685

Lys Ala Leu Ser Asn Gly Ser Leu Pro Ser Gly Thr Gln Leu Arg Arg
        690   695   700

Leu Asp Leu Ser Gly Asn Ser Ile Gly Phe Val Asn Pro Gly Phe Phe
705   710   715   720

Ala Leu Ala Lys Gln Leu Glu Glu Leu Asn Leu Ser Ala Asn Ala Leu
                725   730   735

Lys Thr Val Glu Pro Ser Trp Phe Gly Ser Met Val Gly Asn Leu Lys
                740   745   750

Val Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala Thr
        755   760   765

Phe Val Gly Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu Pro
        770   775   780

Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly His Ser Ile
785   790   795   800

Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Thr Leu Ser Trp Asn
                805   810   815

Cys Phe Gly

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<212>  DNA
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            20                  25                  30


Pro Cys Glu Leu Gln Pro His Gly Gln Val Asp Cys Asn Trp Leu Phe
        35                  40                  45


Leu Lys Ser Val Pro His Phe Ser Ala Gly Ala Pro Arg Ala Asn Val
    50                  55                  60


Thr Ser Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asp Ser
65                  70                  75                  80
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Asp Phe Val His Leu Ser Asn Leu Arg Val Leu Asn Leu Lys Trp Asn
                85   90   95

Cys Pro Pro Ala Gly Leu Ser Pro Met His Phe Pro Cys Arg Met Thr
            100   105   110

Ile Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu Asn
        115   120   125

Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Ala Leu Pro Ser Ser Leu
    130   135   140

Val Ser Leu Ser Leu Ser His Thr Ser Ile Leu Val Leu Gly Pro Thr
145   150   155   160

His Phe Thr Gly Leu His Ala Leu Arg Phe Leu Tyr Met Asp Gly Asn
            165   170   175

Cys Tyr Tyr Met Asn Pro Cys Pro Arg Ala Leu Glu Val Ala Pro Gly
            180   185   190

Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr Asn
    195   200   205

Asn Leu Thr Glu Val Pro Arg Arg Leu Pro Pro Ser Leu Asp Thr Leu
    210   215   220

Leu Leu Ser Tyr Asn His Ile Val Thr Leu Ala Pro Glu Asp Leu Ala
225   230   235   240

Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg Arg
            245   250   255

Cys Asp His Ala Arg Asn Pro Cys Arg Glu Cys Pro Lys Asn Phe Pro
            260   265   270

Lys Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly Leu
    275   280   285

Val Leu Lys Asp Ser Ser Leu Tyr Lys Leu Glu Lys Asp Trp Phe Arg
    290   295   300

Gly Leu Gly Arg Leu Gln Val Leu Asp Leu Ser Glu Asn Phe Leu Tyr

305   310   315   320

Asp Tyr Ile Thr Lys Thr Thr Ile Phe Asn Asp Leu Thr Gln Leu Arg
                325   330   335

Arg Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala His
                340   345   350

Leu His Leu Ala Ser Ser Phe Gly Ser Leu Val Ser Leu Glu Lys Leu
                355   360   365

Asp Met His Gly Ile Phe Phe Arg Ser Leu Thr Asn Ile Thr Leu Gln
        370   375   380

Ser Leu Thr Arg Leu Pro Lys Leu Gln Ser Leu His Leu Gln Leu Asn
385   390   395   400

Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Ala Phe Pro Ser Leu
                405   410   415

Leu Phe Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ala Thr Pro
                420   425   430

Ala Ala Ala Leu Gly Glu Val Asp Ser Arg Val Glu Val Trp Arg Leu
                435   440   445

Pro Arg Gly Leu Ala Pro Gly Pro Leu Asp Ala Val Ser Ser Lys Asp
        450   455   460

Phe Met Pro Ser Cys Asn Leu Asn Phe Thr Leu Asp Leu Ser Arg Asn
465   470   475   480

Asn Leu Val Thr Ile Gln Gln Glu Met Phe Thr Arg Leu Ser Arg Leu
                485   490   495

Gln Cys Leu Arg Leu Ser His Asn Ser Ile Ser Gln Ala Val Asn Gly
                500   505   510

Ser Gln Phe Val Pro Leu Thr Ser Leu Arg Val Leu Asp Leu Ser His
                515   520   525

Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr Glu Leu Pro Gln
        530   535   540

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Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Ser Met Gln
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Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu Pro Ser Leu Arg
            565             570             575


Tyr Leu Ser Leu Ala His Asn Gly Ile His Ser Arg Val Ser Gln Lys
        580             585             590


Leu Ser Ser Ala Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn Ser Leu
        595             600             605


Ser Gln Met Trp Ala Glu Gly Asp Leu Tyr Leu Cys Phe Phe Lys Gly
    610             615             620


Leu Arg Asn Leu Val Gln Leu Asp Leu Ser Glu Asn His Leu His Thr
625             630             635             640


Leu Leu Pro Arg His Leu Asp Asn Leu Pro Lys Ser Leu Arg Gln Leu
            645             650             655


Arg Leu Arg Asp Asn Asn Leu Ala Phe Phe Asn Trp Ser Ser Leu Thr
            660             665             670


Val Leu Pro Arg Leu Glu Ala Leu Asp Leu Ala Gly Asn Gln Leu Lys
        675             680             685


Ala Leu Ser Asn Gly Ser Leu Pro Pro Gly Ile Arg Leu Gln Lys Leu
    690             695             700


Asp Val Ser Ser Asn Ser Ile Gly Phe Val Ile Pro Gly Phe Phe Val
705             710             715             720


Arg Ala Thr Arg Leu Ile Glu Leu Asn Leu Ser Ala Asn Ala Leu Lys
            725             730             735


Thr Val Asp Pro Ser Trp Phe Gly Ser Leu Ala Gly Thr Leu Lys Ile
            740             745             750


Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala Ala Phe
        755             760             765


Val Asp Phe Leu Leu Glu Arg Gln Glu Ala Val Pro Gly Leu Ser Arg
770             775             780
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Arg Val Thr Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg Ser Ile Phe
785   790   795   800

Thr Gln Asp Leu Arg Leu Cys Leu Asp Glu Thr Leu Ser Leu Asp Cys
                 805   810   815

Phe Gly Leu Ser Leu Leu Met Val Ala Leu Gly Leu Ala Val Pro Met
             820   825   830

Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His Leu Cys
         835   840   845

Leu Ala His Leu Pro Arg Arg Arg Gln Arg Gly Glu Asp Thr Leu
     850   855   860

Leu Tyr Asp Ala Val Val Val Phe Asp Lys Val Gln Ser Ala Val Ala
865   870   875   880

Asp Trp Val Tyr Asn Glu Leu Arg Val Gln Leu Glu Glu Arg Arg Gly
             885   890   895

Arg Arg Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp Trp Leu Pro Gly
         900   905   910

Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr Ser Ser Arg Lys
     915   920   925

Thr Met Phe Val Leu Asp His Thr Asp Arg Val Ser Gly Leu Leu Arg
     930   935   940

Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu Asp Arg Lys Asp
945   950   955   960

Val Val Val Leu Val Ile Leu Arg Pro Ala Ala Tyr Arg Ser Arg Tyr
             965   970   975

Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val Leu Leu Trp Pro
         980   985   990

His Gln Pro Ser Gly Gln Gly Ser Phe Trp Ala Asn Leu Gly Ile Ala
         995   1000   1005

Leu Thr Arg Asp Asn Arg His Phe Tyr Asn Arg Asn Phe Cys Arg
     1010   1015   1020

- 28 -

Gly Pro Thr Thr Ala Glu
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<400> 10

Met Gly Pro Tyr Cys Ala Pro His Pro Leu Ser Leu Leu Val Gln Ala
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Ala Ala Leu Ala Ala Ala Leu Ala Glu Gly Thr Leu Pro Ala Phe Leu
            20   25   30

Pro Cys Glu Leu Gln Pro His Gly Gln Val Asp Cys Asn Trp Leu Phe
        35   40   45

Leu Lys Ser Val Pro His Phe Ser Ala Gly Ala Pro Arg Ala Asn Val
    50   55   60

Thr Ser Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asp Ser
65   70   75   80

Asp Phe Val His Leu Ser Asn Leu Arg Val Leu Asn Leu Lys Trp Asn
            85   90   95

Cys Pro Pro Ala Gly Leu Ser Pro Met His Phe Pro Cys Arg Met Thr
            100   105   110

Ile Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu Asn
        115   120   125

Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Ala Leu Pro Ser Ser Leu
    130   135   140

Val Ser Leu Ser Leu Ser His Thr Ser Ile Leu Val Leu Gly Pro Thr
145   150   155   160

His Phe Thr Gly Leu His Ala Leu Arg Phe Leu Tyr Met Asp Gly Asn
            165   170   175

Cys Tyr Tyr Met Asn Pro Cys Pro Arg Ala Leu Glu Val Ala Pro Gly
            180   185   190

Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr Asn
        195   200   205

Asn Leu Thr Glu Val Pro Arg Arg Leu Pro Pro Ser Leu Asp Thr Leu
        210   215   220

Leu Leu Ser Tyr Asn His Ile Val Thr Leu Ala Pro Glu Asp Leu Ala
225   230   235   240

Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg Arg
                245   250   255

Cys Asp His Ala Arg Asn Pro Cys Arg Glu Cys Pro Lys Asn Phe Pro
            260   265   270

Lys Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly Leu
        275   280   285

Val Leu Lys Asp Ser Ser Leu Tyr Lys Leu Glu Lys Asp Trp Phe Arg
        290   295   300

Gly Leu Gly Arg Leu Gln Val Leu Asp Leu Ser Glu Asn Phe Leu Tyr
305   310   315   320

Asp Tyr Ile Thr Lys Thr Thr Ile Phe Asn Asp Leu Thr Gln Leu Arg
                325   330   335

Arg Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala His
            340   345   350

Leu His Leu Ala Ser Ser Phe Gly Ser Leu Val Ser Leu Glu Lys Leu
        355   360   365

Asp Met His Gly Ile Phe Phe Arg Ser Leu Thr Asn Ile Thr Leu Gln
        370   375   380

Ser Leu Thr Arg Leu Pro Lys Leu Gln Ser Leu His Leu Gln Leu Asn
385   390   395   400

Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Ala Phe Pro Ser Leu
                405   410   415

Leu Phe Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ala Thr Pro

- 30 -

```
                    420                    425                    430


     Ala Ala Ala Leu Gly Glu Val Asp Ser Arg Val Glu Val Trp Arg Leu
             435                 440                 445


     Pro Arg Gly Leu Ala Pro Gly Pro Leu Asp Ala Val Ser Ser Lys Asp
             450                 455                 460


     Phe Met Pro Ser Cys Asn Leu Asn Phe Thr Leu Asp Leu Ser Arg Asn
     465                 470                 475                 480


     Asn Leu Val Thr Ile Gln Gln Glu Met Phe Thr Arg Leu Ser Arg Leu
                     485                 490                 495


     Gln Cys Leu Arg Leu Ser His Asn Ser Ile Ser Gln Ala Val Asn Gly
                 500                 505                 510


     Ser Gln Phe Val Pro Leu Thr Ser Leu Arg Val Leu Asp Leu Ser His
             515                 520                 525


     Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr Glu Leu Pro Gln
             530                 535                 540


     Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Ser Met Gln
     545                 550                 555                 560


     Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu Pro Ser Leu Arg
                     565                 570                 575


     Tyr Leu Ser Leu Ala His Asn Gly Ile His Ser Arg Val Ser Gln Lys
                 580                 585                 590


     Leu Ser Ser Ala Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn Ser Leu
                 595                 600                 605


     Ser Gln Met Trp Ala Glu Gly Asp Leu Tyr Leu Cys Phe Phe Lys Gly
             610                 615                 620


     Leu Arg Asn Leu Val Gln Leu Asp Leu Ser Glu Asn His Leu His Thr
     625                 630                 635                 640


     Leu Leu Pro Arg His Leu Asp Asn Leu Pro Lys Ser Leu Arg Gln Leu
                 645                 650                 655
```

```
Arg Leu Arg Asp Asn Asn Leu Ala Phe Phe Asn Trp Ser Ser Leu Thr
            660             665             670


Val Leu Pro Arg Leu Glu Ala Leu Asp Leu Ala Gly Asn Gln Leu Lys
            675             680             685


Ala Leu Ser Asn Gly Ser Leu Pro Pro Gly Ile Arg Leu Gln Lys Leu
            690             695             700


Asp Val Ser Ser Asn Ser Ile Gly Phe Val Ile Pro Gly Phe Phe Val
705             710             715             720


Arg Ala Thr Arg Leu Ile Glu Leu Asn Leu Ser Ala Asn Ala Leu Lys
                725             730             735


Thr Val Asp Pro Ser Trp Phe Gly Ser Leu Ala Gly Thr Leu Lys Ile
            740             745             750


Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala Ala Phe
            755             760             765


Val Asp Phe Leu Leu Glu Arg Gln Glu Ala Val Pro Gly Leu Ser Arg
    770             775             780


Arg Val Thr Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg Ser Ile Phe
785             790             795             800


Thr Gln Asp Leu Arg Leu Cys Leu Asp Glu Thr Leu Ser Leu Asp Cys
            805             810             815


Phe Gly
```

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<210>   11
<211>   3191
<212>   DNA
<213>   Bos taurus

<400>   11
gggaagtggg cgccaagcat ccttccctgc agctgcctcc caacctgccc gccagaccct      60

ctggagaagc cgcattccct gtcatgggcc cctactgtgc cccgcacccc ctttctctcc     120

tggtgcaggc ggcggcactg gcagcggccc tggccgaggg caccctgcct gccttcctgc     180

cctgtgagct ccagccccat ggtcaggtgg actgcaactg gctgttcctg aagtctgtgc     240

cgcactttc ggctggagcc ccccgggcca atgtcaccag cctctcctta atctccaacc     300
```

```
gcatccacca cttgcatgac tctgacttcg tccacctgtc caacctgcgg gtcctcaacc    360

tcaagtggaa ctgcccgccg gccggcctca gccccatgca cttcccctgc cgtatgacca    420

tcgagcccaa caccttcctg gctgtgccca ccctggagga gctgaacctg agctacaacg    480

gcatcacgac cgtgcctgcc ctgcccagtt ccctcgtgtc cctgtcgctg agccacacca    540

gcatcctggt gctaggcccc acccacttca ccggcctgca cgccctgcgc tttctgtaca    600

tggacggcaa ctgctactac atgaacccct gcccgcgggc cctggaggtg gccccaggcg    660

ccctcctcgg cctgggcaac ctcacgcacc tgtcgctcaa gtacaacaac ctcacggagg    720

tgccccgccg cctgcccccc agcctggaca ccctgctgct gtcctacaac cacattgtca    780

ccctggcacc cgaggacctg gccaacctga ctgccctgcg cgtgcttgac gtgggtggga    840

actgccgccg ctgcgaccat gcccgcaacc cctgcaggga gtgcccaaag aacttcccca    900

agctgcaccc tgacaccttc agtcacctga ccgcctcga aggcctggtg ttgaaggaca    960

gttctctcta caaactagag aaagattggt tccgcggcct gggcaggctc caagtgctcg    1020

acctgagtga gaacttcctc tatgactaca tcaccaagac caccatcttc aacgacctga    1080

cccagctgcg cagactcaac ctgtccttca attaccacaa gaaggtgtcc ttcgcccacc    1140

tgcacctagc gtcctccttt gggagtctgg tgtccctgga gaagctggac atgcacggca    1200

tcttcttccg ctccctcacc aacatcacgc tccagtcgct gacccggctg cccaagctcc    1260

agagtctgca tctgcagctg aacttcatca accaggccca gctcagcatc tttggggcct    1320

tcccgagcct gctcttcgtg gacctgtcgg acaaccgcat cagcggagcc gcgacgccag    1380

cggccgccct gggggaggtg gacagcaggg tggaagtctg gcgattgccc aggggcctcg    1440

ctccaggccc gctggacgcc gtcagctcaa aggacttcat gccaagctgc aacctcaact    1500

tcaccttgga cctgtcacgg aacaacctgg tgacaatcca gcaagagatg tttacccgcc    1560

tctcccgcct ccagtgcctg cgcctgagcc acaacagcat ctcgcaggcg gttaatggct    1620

cccagttcgt gccgctgacc agcctgcgag tgctcgacct gtcccacaac aagctggacc    1680

tgtaccatgg cgcgctcatt c acggagctgc cgcagctgga ggcactggac ctcagctaca    1740

acagccagcc cttcagcatg cagggcgtgg gccacaacct cagcttcgtg cccagctgc    1800

cctccctgcg ctacctcagc cttgcgcaca atggcatcca cagccgcgtg tcacagaagc    1860

tcagcagcgc ctcgttgcgc gccctggact tcagcggcaa ctccctgagc cagatgtggg    1920

ccgagggaga cctctatctc tgctttttca aaggcttgag gaacctggtc cagctggacc    1980

tgtccgagaa ccatctgcac accctcctgc ctcgtcacct ggacaacctg cccaagagcc    2040
```

                                          - 33 -

```
tgcggcagct gcgtctccgg gacaataacc tggccttctt caactggagc agcctgaccg    2100

tcctgccccg gctggaagcc ctggatctgg caggaaacca gctgaaggcc ctgagcaacg    2160

gcagcctgcc gcctggcatc cggctccaga agctggacgt gagcagcaac agcatcggct    2220

tcgtgatccc cggcttcttc gtccgcgcga ctcggctgat agagcttaac ctcagcgcca    2280

atgccctgaa gacagtggat ccctcctggt tcggttcctt agcagggacc ctgaaaatcc    2340

tagacgtgag cgccaacccg ctccactgcg cctgcggggc ggcctttgtg gacttcctgc    2400

tggagagaca ggaggccgtg cccgggctgt ccaggcgcgt cacatgtggc agtccgggcc    2460

agctccaggg ccgcagcatc ttcacacagg acctgcgcct ctgcctggat gagaccctct    2520

ccttggactg ctttggcctc tcactgctaa tggtggcgct gggcctggca gtgcccatgc    2580

tgcaccacct ctgtggctgg gacctctggt actgcttcca cctgtgtctg gcccatttgc    2640

cccgacggcg gcggcagcgg ggcgaggaca ccctgctcta tgatgccgtc gtggtcttcg    2700

acaaggtgca gagtgcagtg gctgattggg tgtacaacga gctccgcgtg cagctggagg    2760

agcgccgggg gcgccgggcg ctccgcctct gcctggagga gcgagactgg ctccctggta    2820

agacgctctt cgagaacctg tgggcctcgg tctacagcag ccgcaagacc atgttcgtgc    2880

tggaccacac ggaccgggtc agcggcctcc tgcgcgccag cttcctgctg gcccagcagc    2940

gcctgttgga ggaccgcaag gacgtcgtag tgctggtgat cctgcgcccc gccgcctatc    3000

ggtcccgcta cgtgcggctg cgccagcgcc tctgccgcca gagcgtcctc ctctggcccc    3060

accagcccag tggccagggt agtttctggg ccaacctggg catagccctg accagggaca    3120

accgtcactt ctataaccgg aacttctgcc ggggccccac gacagccgaa tagcacagag    3180

tgactgccca g                                                          3191
```

```
<210>  12
<211>  2454
<212>  DNA
<213>  Bos taurus

<400>  12
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gcggccctgg ccgagggcac cctgcctgcc ttcctgccct gtgagctcca gccccatggt    120

caggtggact gcaactggct gttcctgaag tctgtgccgc acttttcggc tggagccccc    180

cgggccaatg tcaccagcct ctccttaatc tccaaccgca tccaccactt gcatgactct    240

gacttcgtcc acctgtccaa cctgcgggtc ctcaacctca agtggaactg cccgccggcc    300

ggcctcagcc ccatgcactt cccctgccgt atgaccatcg agcccaacac cttcctggct    360
```

```
gtgcccaccc tggaggagct gaacctgagc tacaacggca tcacgaccgt gcctgccctg      420

cccagttccc tcgtgtccct gtcgctgagc cacaccagca tcctggtgct aggccccacc      480

cacttcaccg gcctgcacgc cctgcgcttt ctgtacatgg acggcaactg ctactacatg      540

aaccccctgcc cgcgggccct ggaggtggcc ccaggcgccc tcctcggcct gggcaacctc      600

acgcacctgt cgctcaagta caacaacctc acggaggtgc ccgccgcct gccccccagc      660

ctggacaccc tgctgctgtc ctacaaccac attgtcaccc tggcacccga ggacctggcc      720

aacctgactg ccctgcgcgt gcttgacgtg ggtgggaact gccgccgctg cgaccatgcc      780

cgcaaccccct gcagggagtg cccaaagaac ttccccaagc tgcaccctga caccttcagt      840

cacctgagcc gcctcgaagg cctggtgttg aaggacagtt ctctctacaa actagagaaa      900

gattggttcc gcggcctggg caggctccaa gtgctcgacc tgagtgagaa cttcctctat      960

gactacatca ccaagaccac catcttcaac gacctgaccc agctgcgcag actcaacctg     1020

tccttcaatt accacaagaa ggtgtccttc gcccacctgc acctagcgtc ctcctttggg     1080

agtctggtgt ccctggagaa gctggacatg cacggcatct tcttccgctc cctcaccaac     1140

atcacgctcc agtcgctgac ccggctgccc aagctccaga gtctgcatct gcagctgaac     1200

ttcatcaacc aggcccagct cagcatcttt ggggccttcc cgagcctgct cttcgtggac     1260

ctgtcggaca accgcatcag cggagccgcg acgccagcgg ccgccctggg ggaggtggac     1320

agcagggtgg aagtctggcg attgcccagg ggcctcgctc caggcccgct ggacgccgtc     1380

agctcaaagg acttcatgcc aagctgcaac ctcaacttca ccttggacct gtcacggaac     1440

aacctggtga caatccagca agagatgttt acccgcctct cccgcctcca gtgcctgcgc     1500

ctgagccaca acagcatctc gcaggcggtt aatggctccc agttcgtgcc gctgaccagc     1560

ctgcgagtgc tcgacctgtc ccacaacaag ctggacctgt accatgggcg ctcattcacg     1620

gagctgccgc agctggaggc actggacctc agctacaaca gccagccctt cagcatgcag     1680

ggcgtgggcc acaacctcag cttcgtggcc cagctgccct cctgcgcta cctcagcctt     1740

gcgcacaatg gcatccacag ccgcgtgtca cagaagctca gcagcgcctc gttgcgcgcc     1800

ctggacttca gcggcaactc cctgagccag atgtgggccg agggagacct ctatctctgc     1860

tttttcaaag gcttgaggaa cctggtccag ctggacctgt ccgagaacca tctgcacacc     1920

ctcctgcctc gtcacctgga caacctgccc aagagcctgc ggcagctgcg tctccgggac     1980

aataacctgg ccttcttcaa ctggagcagc ctgaccgtcc tgccccggct ggaagccctg     2040

gatctggcag gaaaccagct gaaggccctg agcaacggca gcctgccgcc tggcatccgg     2100

ctccagaagc tggacgtgag cagcaacagc atcggcttcg tgatccccgg cttcttcgtc     2160
```

```
cgcgcgactc ggctgataga gcttaacctc agcgccaatg ccctgaagac agtggatccc   2220

tcctggttcg gttccttagc agggaccctg aaaatcctag acgtgagcgc caacccgctc   2280

cactgcgcct gcggggcggc ctttgtggac ttcctgctgg agagacagga ggccgtgccc   2340

gggctgtcca ggcgcgtcac atgtggcagt ccgggccagc tccagggccg cagcatcttc   2400

acacaggacc tgcgcctctg cctggatgag accctctcct tggactgctt tggc          2454
```

<210> 13
<211> 1031
<212> PRT
<213> Equus caballus

<400> 13

```
Met Gly Pro Cys His Gly Ala Leu Gln Pro Leu Ser Leu Leu Val Gln
1               5                   10                  15


Ala Ala Met Leu Ala Val Ala Leu Ala Gln Gly Thr Leu Pro Pro Phe
            20                  25                  30


Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu
        35                  40                  45


Phe Leu Lys Ser Val Pro His Phe Ser Ala Ala Ala Pro Arg Asp Asn
    50                  55                  60


Val Thr Ser Leu Ser Leu Leu Ser Asn Arg Ile His His Leu His Asp
65                  70                  75                  80


Ser Asp Phe Ala Gln Leu Ser Asn Leu Gln Lys Leu Asn Leu Lys Trp
                85                  90                  95


Asn Cys Pro Pro Ala Gly Leu Ser Pro Met His Phe Pro Cys His Met
            100                 105                 110


Thr Ile Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu
        115                 120                 125


Asn Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Ala Leu Pro Ser Ser
    130                 135                 140


Leu Val Ser Leu Ile Leu Ser Arg Thr Asn Ile Leu Gln Leu Asp Pro
145                 150                 155                 160
```

Thr Ser Leu Thr Gly Leu His Ala Leu Arg Phe Leu Tyr Met Asp Gly
                165   170   175

Asn Cys Tyr Tyr Lys Asn Pro Cys Gly Arg Ala Leu Glu Val Ala Pro
                180   185   190

Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr
                195   200   205

Asn Asn Leu Thr Thr Val Pro Arg Ser Leu Pro Pro Ser Leu Glu Tyr
    210   215   220

Leu Leu Leu Ser Tyr Asn His Ile Val Thr Leu Ala Pro Glu Asp Leu
225   230   235   240

Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
                245   250   255

Arg Cys Asp His Ala Arg Asn Pro Cys Val Glu Cys Pro His Lys Phe
                260   265   270

Pro Gln Leu His Ser Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly
                275   280   285

Leu Val Leu Lys Asp Ser Ser Leu Tyr Gln Leu Asn Pro Arg Trp Phe
                290   295   300

Arg Gly Leu Gly Asn Leu Thr Val Leu Asp Leu Ser Glu Asn Phe Leu
305   310   315   320

Tyr Asp Cys Ile Thr Lys Thr Lys Ala Phe Gln Gly Leu Ala Gln Leu
                325   330   335

Arg Arg Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala
                340   345   350

His Leu Thr Leu Ala Pro Ser Phe Gly Ser Leu Leu Ser Leu Gln Glu
                355   360   365

Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Ser Gln Lys Thr Leu
    370   375   380

Gln Pro Leu Ala Arg Leu Pro Met Leu Gln Arg Leu Tyr Leu Gln Met
385   390   395   400

Asn Phe Ile Asn Gln Ala Gln Leu Gly Ile Phe Lys Asp Phe Pro Gly
            405   410   415

Leu Arg Tyr Ile Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Val Glu
            420   425   430

Pro Val Ala Thr Thr Gly Glu Val Asp Gly Gly Lys Lys Val Trp Leu
            435   440   445

Thr Ser Arg Asp Leu Thr Pro Gly Pro Leu Asp Thr Pro Ser Ser Glu
    450   455   460

Asp Phe Met Pro Ser Cys Lys Asn Leu Ser Phe Thr Leu Asp Leu Ser
465   470   475   480

Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Ala Gln Leu Ser
                485   490   495

Arg Leu Gln Cys Leu Arg Leu Ser His Asn Ser Ile Ser Gln Ala Val
            500   505   510

Asn Gly Ser Gln Phe Val Pro Leu Thr Ser Leu Gln Val Leu Asp Leu
            515   520   525

Ser His Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr Glu Leu
    530   535   540

Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Ser
545   550   555   560

Met Arg Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu Pro Thr
                565   570   575

Leu Arg Tyr Leu Ser Leu Ala His Asn Gly Ile His Ser Arg Val Ser
            580   585   590

Gln Gln Leu Cys Ser Thr Ser Leu Trp Ala Leu Asp Phe Ser Gly Asn
            595   600   605

Ser Leu Ser Gln Met Trp Ala Glu Gly Asp Leu Tyr Leu Arg Phe Phe
    610   615   620

Gln Gly Leu Arg Ser Leu Ile Arg Leu Asp Leu Ser Gln Asn Arg Leu
625   630   635   640

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His Thr Leu Leu Pro Cys Thr Leu Gly Asn Leu Pro Lys Ser Leu Gln
                  645   650   655

Leu Leu Arg Leu Arg Asn Asn Tyr Leu Ala Phe Phe Asn Trp Ser Ser
              660   665   670

Leu Thr Leu Leu Pro Asn Leu Glu Thr Leu Asp Leu Ala Gly Asn Gln
          675   680   685

Leu Lys Ala Leu Ser Asn Gly Ser Leu Pro Ser Gly Thr Gln Leu Gln
          690   695   700

Arg Leu Asp Val Ser Arg Asn Ser Ile Ile Phe Val Val Pro Gly Phe
705   710   715   720

Phe Ala Leu Ala Thr Arg Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala
              725   730   735

Leu Arg Thr Glu Glu Pro Ser Trp Phe Gly Phe Leu Ala Gly Ser Leu
          740   745   750

Glu Val Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala
          755   760   765

Ala Phe Val Asp Phe Leu Leu Gln Val Gln Ala Ala Val Pro Gly Leu
    770   775   780

Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg Ser
785   790   795   800

Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Lys Ser Leu Ser Trp
              805   810   815

Asp Cys Phe Gly Leu Ser Leu Leu Val Val Ala Leu Gly Leu Ala Met
          820   825   830

Pro Met Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His
          835   840   845

Leu Gly Leu Ala Trp Leu Pro Arg Arg Gly Trp Gln Arg Gly Ala Asp
    850   855   860

Ala Leu Ser Tyr Asp Ala Phe Val Val Phe Asp Lys Ala Gln Ser Ala

865   870   875   880

Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Val Arg Leu Glu Glu Arg
              885   890   895

Arg Gly Arg Arg Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp Trp Leu
          900   905   910

Pro Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr Ser Ser
          915   920   925

Arg Lys Met Leu Phe Val Leu Ala His Thr Asp Gln Val Ser Gly Leu
      930   935   940

Leu Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu Asp Arg
945   950   955   960

Lys Asp Val Val Val Leu Val Ile Leu Ser Pro Asp Ala Arg Arg Ser
              965   970   975

Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val Leu Phe
          980   985   990

Trp Pro His Gln Pro Ser Gly Gln Arg Ser Phe Trp Ala Gln Leu Gly
      995   1000   1005

Met Ala Leu Thr Arg Asp Asn Arg His Phe Tyr Asn Gln Asn Phe
      1010   1015   1020

Cys Arg Gly Pro Thr Met Ala Glu
      1025   1030

<210> 14
<211> 820
<212> PRT
<213> Equus caballus

<400> 14

Met Gly Pro Cys His Gly Ala Leu Gln Pro Leu Ser Leu Leu Val Gln
1   5   10   15

Ala Ala Met Leu Ala Val Ala Leu Ala Gln Gly Thr Leu Pro Pro Phe
          20   25   30

Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu

                35   40   45

    Phe Leu Lys Ser Val Pro His Phe Ser Ala Ala Ala Pro Arg Asp Asn
        50   55   60

    Val Thr Ser Leu Ser Leu Leu Ser Asn Arg Ile His His Leu His Asp
    65   70   75   80

    Ser Asp Phe Ala Gln Leu Ser Asn Leu Gln Lys Leu Asn Leu Lys Trp
                    85   90   95

    Asn Cys Pro Pro Ala Gly Leu Ser Pro Met His Phe Pro Cys His Met
                100   105   110

    Thr Ile Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu
            115   120   125

    Asn Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Ala Leu Pro Ser Ser
        130   135   140

    Leu Val Ser Leu Ile Leu Ser Arg Thr Asn Ile Leu Gln Leu Asp Pro
    145   150   155   160

    Thr Ser Leu Thr Gly Leu His Ala Leu Arg Phe Leu Tyr Met Asp Gly
                165   170   175

    Asn Cys Tyr Tyr Lys Asn Pro Cys Gly Arg Ala Leu Glu Val Ala Pro
                180   185   190

    Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr
            195   200   205

    Asn Asn Leu Thr Thr Val Pro Arg Ser Leu Pro Pro Ser Leu Glu Tyr
        210   215   220

    Leu Leu Leu Ser Tyr Asn His Ile Val Thr Leu Ala Pro Glu Asp Leu
    225   230   235   240

    Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
                245   250   255

    Arg Cys Asp His Ala Arg Asn Pro Cys Val Glu Cys Pro His Lys Phe
                260   265   270

```
Pro Gln Leu His Ser Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly
        275             280             285
```

```
Leu Val Leu Lys Asp Ser Ser Leu Tyr Gln Leu Asn Pro Arg Trp Phe
        290             295             300
```

```
Arg Gly Leu Gly Asn Leu Thr Val Leu Asp Leu Ser Glu Asn Phe Leu
305             310             315             320
```

```
Tyr Asp Cys Ile Thr Lys Thr Lys Ala Phe Gln Gly Leu Ala Gln Leu
                325             330             335
```

```
Arg Arg Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala
            340             345             350
```

```
His Leu Thr Leu Ala Pro Ser Phe Gly Ser Leu Leu Ser Leu Gln Glu
        355             360             365
```

```
Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Ser Gln Lys Thr Leu
        370             375             380
```

```
Gln Pro Leu Ala Arg Leu Pro Met Leu Gln Arg Leu Tyr Leu Gln Met
385             390             395             400
```

```
Asn Phe Ile Asn Gln Ala Gln Leu Gly Ile Phe Lys Asp Phe Pro Gly
                405             410             415
```

```
Leu Arg Tyr Ile Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Val Glu
            420             425             430
```

```
Pro Val Ala Thr Thr Gly Glu Val Asp Gly Gly Lys Lys Val Trp Leu
        435             440             445
```

```
Thr Ser Arg Asp Leu Thr Pro Gly Pro Leu Asp Thr Pro Ser Ser Glu
        450             455             460
```

```
Asp Phe Met Pro Ser Cys Lys Asn Leu Ser Phe Thr Leu Asp Leu Ser
465             470             475             480
```

```
Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Ala Gln Leu Ser
                485             490             495
```

```
Arg Leu Gln Cys Leu Arg Leu Ser His Asn Ser Ile Ser Gln Ala Val
            500             505             510
```

Asn Gly Ser Gln Phe Val Pro Leu Thr Ser Leu Gln Val Leu Asp Leu
        515   520   525

Ser His Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr Glu Leu
        530   535   540

Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Ser
545   550   555   560

Met Arg Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu Pro Thr
                565   570   575

Leu Arg Tyr Leu Ser Leu Ala His Asn Gly Ile His Ser Arg Val Ser
            580   585   590

Gln Gln Leu Cys Ser Thr Ser Leu Trp Ala Leu Asp Phe Ser Gly Asn
            595   600   605

Ser Leu Ser Gln Met Trp Ala Glu Gly Asp Leu Tyr Leu Arg Phe Phe
    610   615   620

Gln Gly Leu Arg Ser Leu Ile Arg Leu Asp Leu Ser Gln Asn Arg Leu
625   630   635   640

His Thr Leu Leu Pro Cys Thr Leu Gly Asn Leu Pro Lys Ser Leu Gln
                645   650   655

Leu Leu Arg Leu Arg Asn Asn Tyr Leu Ala Phe Phe Asn Trp Ser Ser
            660   665   670

Leu Thr Leu Leu Pro Asn Leu Glu Thr Leu Asp Leu Ala Gly Asn Gln
            675   680   685

Leu Lys Ala Leu Ser Asn Gly Ser Leu Pro Ser Gly Thr Gln Leu Gln
        690   695   700

Arg Leu Asp Val Ser Arg Asn Ser Ile Ile Phe Val Val Pro Gly Phe
705   710   715   720

Phe Ala Leu Ala Thr Arg Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala
                725   730   735

Leu Arg Thr Glu Glu Pro Ser Trp Phe Gly Phe Leu Ala Gly Ser Leu
            740   745   750

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```
Glu Val Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala
        755             760             765
```

```
Ala Phe Val Asp Phe Leu Leu Gln Val Gln Ala Ala Val Pro Gly Leu
        770             775             780
```

```
Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg Ser
785             790             795             800
```

```
Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Lys Ser Leu Ser Trp
            805             810             815
```

```
Asp Cys Phe Gly
        820
```

```
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<211>  3391
<212>  DNA
<213>  Equus caballus

<400>  15
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ccttgccatg gtgccctgca gccctgtct ctcctggtgc aggcggccat gctggccgtg     180

gctctggccc aaggcaccct gcctcccttc ctgccctgtg agctccagcc ccacggcctg     240

gtgaactgca actggctgtt cctgaagtcc gtgccccact tctcagcagc agcaccccgg     300

gacaatgtca ccagccttc cttgctctcc aaccgcatcc accacctcca cgactccgac     360

tttgcccaac tgtccaacct gcagaaactc aacctcaaat ggaactgccc gccagccggc     420

ctcagcccca tgcacttccc ctgccacatg accatcgagc ccaacacttt cctggctgta     480

cccaccctgg aggagctgaa cctgagctac aacggcatca cgactgtgcc tgccctgccc     540

agctccctcg tgtccctgat cctgagccgc accaacatcc tgcagctaga ccccaccagc     600

ctcacgggcc tgcatgccct gcgcttccta tacatggatg caactgcta ctacaagaac     660

ccctgcgggc gggccctgga ggtggcccca ggcgccctcc ttggcctggg caacctcacc     720

cacctgtcac tcaagtacaa caacctcaca cggtgcccc gcagcctgcc cctagcctg     780

gagtacctgc tgttgtccta caaccacatt gtcaccctgg cacctgagga cctggccaat     840

ctgactgccc tgcgtgtgct cgatgtgggt ggaaactgcc gccgctgtga ccatgcacgc     900

aaccccctgcg tggagtgccc acataaattc ccccagctgc actccgacac cttcagccac     960
```

```
ctaagccgcc tagaaggcct cgtgttgaag gatagttctc tctaccagct gaaccccaga    1020

tggttccgtg gcctgggcaa cctcacagtg ctcgacctga gtgagaactt cctctacgac    1080

tgcatcacca aaaccaaggc attccagggc ctggcccagc tgcgaagact caacttgtcc    1140

ttcaattacc ataagaaggt gtccttcgcc cacctgacgc tggcaccctc cttcgggagc    1200

ctgctctccc tgcaggaact ggacatgcat ggcatcttct ccgctcact cagccagaag     1260

acgctccagc cactggcccg cctgcccatg ctccagcgtc tgtatctgca gatgaacttc    1320

atcaaccagg cccagctcgg catcttcaag gacttccctg gtctgcgcta catagacctg    1380

tcagacaacc gcatcagtgg agctgtggag ccggtggcca ccacagggga ggtggatggt    1440

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aacctggtaa cagtccagcc agagatgttt gcccagctct cgcgcctcca gtgcctgcgc    1620

ctgagccaca acagcatctc gcaggcggtc aatggctcac agttcgtgcc actgaccagc    1680

ctgcaggtgc tggacctgtc ccataacaaa ctggacctgt accatgggcg ctcgtttacg    1740

gagctgccgc gactggaggc cctggacctc agctacaaca gccagccctt cagcatgcgg    1800

ggtgtgggcc acaacctcag ctttgtggcc cagctgccca ccctgcgcta cctcagcctg    1860

gcacacaatg gcatccacag ccgtgtgtcc cagcagctct gcagcacctc gctgtgggcc    1920

ctggacttca gcggcaattc cctgagccag atgtgggctg agggagacct ctatctccgc    1980

ttcttccaag gcctgagaag cctaatccgg ctagacctgt cccagaatcg tctgcatacc    2040

ctcctgccat gcaccctggg caacctcccc aagagcttgc agctgctgcg tctccgtaac    2100

aattacctgg ccttcttcaa ttggagcagc ctgaccctcc tgcccaacct ggaaaccctg    2160

gacctggctg aaaccagct gaaggctctg agcaatggca gcctgccttc tggcacccag    2220

ctccagaggc tggacgtcag caggaacagc atcatcttcg tggtccctgg cttctttgct    2280

ctggccacga ggctgcgaga gctcaacctc agtgccaacg ccctcaggac agaggagccc    2340

tcctggtttg gtttcctagc aggctccctt gaagtcctag atgtgagcgc caaccctctg    2400

cactgcgcct gtggggcagc ctttgtggac ttcctgctgc aggttcaggc tgccgtgcct    2460

ggtctgccca gccgcgtcaa gtgtggcagt ccgggccagc tccagggccg cagcatcttc    2520

gcacaagacc tgcgcctctg cctggacaag tccctctcct gggactgttt tggtctctca    2580

ttgctggttg tggccctggg cctggccatg cctatgttgc accacctctg cggctgggac    2640

ctctggtact gcttccacct gggcctggcc tggctgcccc ggcggggggtg gcagcggggc    2700
```

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gcggatgccc tgagctatga tgcctttgtg gtcttcgaca aggcacagag cgcagtggcc      2760

gactgggtgt acaatgaact gcgggtgcgg ctagaggagc gccgtgggcg ccgggcgctc      2820

cgcctgtgtc tggaggagcg tgactggcta cctggcaaga cgctgttcga aaacctgtgg      2880

gcctcagtct acagcagccg caagatgctg tttgtgctgg cccacacgga ccaggtcagt      2940

ggcctcttgc gtgccagctt cctgctggcc cagcagcgtc tgctggagga ccgcaaggac      3000

gttgtggtgc tggtaatcct gagccctgac gcccgccgtt cccgttacgt gcggctgcgc      3060

cagcgcctct gccgccagag tgtcctcttc tggccccacc agcctagtgg ccagcgcagc      3120

ttctgggccc agctaggcat ggccctgacc agggacaacc gccacttcta taaccagaac      3180

ttctgccggg gcccgacgat ggctgagtag cacagagtga cagcctggca tgtacaaccc      3240

ccagccctga ccttgcctct ctgcctatga tgcccagtct gcctcactct gtgacgcccc      3300

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caggccaaac agccaaaaaa aaaaaaaaaa a                                     3391
```

<210> 16
<211> 2460
<212> DNA
<213> Equus caballus

<400> 16

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gccgtggctc tggcccaagg caccctgcct cccttcctgc cctgtgagct ccagccccac       120

ggcctggtga actgcaactg gctgttcctg aagtccgtgc cccacttctc agcagcagca       180

ccccgggaca atgtcaccag cctttccttg ctctccaacc gcatccacca cctccacgac       240

tccgactttg cccaactgtc caacctgcag aaactcaacc tcaaatggaa ctgcccgcca       300

gccggcctca gccccatgca cttcccctgc cacatgacca tcgagcccaa cactttcctg       360

gctgtaccca ccctggagga gctgaacctg agctacaacg gcatcacgac tgtgcctgcc       420

ctgcccagct ccctcgtgtc cctgatcctg agccgcacca acatcctgca gctagacccc       480

accagcctca cgggcctgca tgccctgcgc ttcctataca tggatggcaa ctgctactac       540

aagaacccct gcgggcgggc cctggaggtg gccccaggcg ccctccttgg cctgggcaac       600

ctcacccacc tgtcactcaa gtacaacaac ctcacaacgg tgccccgcag cctgccccct       660

agcctggagt acctgctgtt gtcctacaac cacattgtca ccctggcacc tgaggacctg       720

gccaatctga ctgccctgcg tgtgctcgat gtgggtggaa actgccgccg ctgtgaccat       780

gcacgcaacc cctgcgtgga gtgcccacat aaattccccc agctgcactc cgacaccttc       840
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cccagatggt tccgtggcct gggcaacctc acagtgctcg acctgagtga gaacttcctc      960

tacgactgca tcaccaaaac caaggcattc cagggcctgg cccagctgcg aagactcaac     1020

ttgtccttca attaccataa gaaggtgtcc ttcgcccacc tgacgctggc accctccttc     1080

gggagcctgc tctccctgca ggaactggac atgcatggca tcttcttccg ctcactcagc     1140

cagaagacgc tccagccact ggcccgcctg cccatgctcc agcgtctgta tctgcagatg     1200

aacttcatca accaggccca gctcggcatc ttcaaggact tccctggtct gcgctacata     1260

gacctgtcag acaaccgcat cagtggagct gtggagccgg tggccaccac aggggaggtg     1320

gatggtggga agaaggtctg gctgacatcc agggacctca ctccaggccc actggacacc     1380

cccagctctg aggacttcat gccaagctgc aagaacctca gcttcacctt ggacctgtca     1440

cggaacaacc tggtaacagt ccagccagag atgtttgccc agctctcgcg cctccagtgc     1500

ctgcgcctga gccacaacag catctcgcag gcggtcaatg gctcacagtt cgtgccactg     1560

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tttacggagc tgccgcgact ggaggccctg gacctcagct acaacagcca gcccttcagc     1680

atgcggggtg tgggccacaa cctcagcttt gtggcccagc tgcccaccct gcgctacctc     1740

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ctccgcttct tccaaggcct gagaagccta atccggctag acctgtccca gaatcgtctg     1920

cataccctcc tgccatgcac cctgggcaac ctccccaaga gcttgcagct gctgcgtctc     1980

cgtaacaatt acctggcctt cttcaattgg agcagcctga ccctcctgcc caacctggaa     2040

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acccagctcc agaggctgga cgtcagcagg aacagcatca tcttcgtggt ccctggcttc     2160

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gagccctcct ggtttggttt cctagcaggc tcccttgaag tcctagatgt gagcgccaac     2280

cctctgcact gcgcctgtgg ggcagccttt gtggacttcc tgctgcaggt tcaggctgcc     2340

gtgcctggtc tgcccagccg cgtcaagtgt ggcagtccgg gccagctcca gggccgcagc     2400

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```

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<211>   1029
<212>   PRT
<213>   Ovis aries
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<400> 17

Met Gly Pro Tyr Cys Ala Pro His Pro Leu Ser Leu Leu Val Gln Ala
1   5   10   15

Ala Ala Leu Ala Ala Ala Leu Ala Gln Gly Thr Leu Pro Ala Phe Leu
            20   25   30

Pro Cys Glu Leu Gln Pro Arg Gly Lys Val Asn Cys Asn Trp Leu Phe
            35   40   45

Leu Lys Ser Val Pro Arg Phe Ser Ala Gly Ala Pro Arg Ala Asn Val
        50   55   60

Thr Ser Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asp Ser
65   70   75   80

Asp Phe Val His Leu Ser Asn Leu Arg Val Leu Asn Leu Lys Trp Asn
                85   90   95

Cys Pro Pro Ala Gly Leu Ser Pro Met His Phe Pro Cys Arg Met Thr
            100   105   110

Ile Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu Asn
            115   120   125

Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Ala Leu Pro Ser Ser Leu
        130   135   140

Val Ser Leu Ser Leu Ser Arg Thr Ser Ile Leu Val Leu Gly Pro Thr
145   150   155   160

His Phe Thr Gly Leu His Ala Leu Arg Phe Leu Tyr Met Asp Gly Asn
            165   170   175

Cys Tyr Tyr Lys Asn Pro Cys Gln Gln Ala Val Glu Val Ala Pro Gly
            180   185   190

Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr Asn
        195   200   205

Asn Leu Thr Glu Val Pro Arg Arg Leu Pro Pro Ser Leu Asp Thr Leu
210   215   220

Leu Leu Ser Tyr Asn His Ile Ile Thr Leu Ala Pro Glu Asp Leu Ala
225   230   235   240

Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg Arg
                245   250   255

Cys Asp His Ala Arg Asn Pro Cys Arg Glu Cys Pro Lys Asn Phe Pro
            260   265   270

Lys Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly Leu
        275   280   285

Val Leu Lys Asp Ser Ser Leu Tyr Lys Leu Glu Lys Asp Trp Phe Arg
    290   295   300

Gly Leu Gly Arg Leu Gln Val Leu Asp Leu Ser Glu Asn Phe Leu Tyr
305   310   315   320

Asp Tyr Ile Thr Lys Thr Thr Ile Phe Arg Asn Leu Thr Gln Leu Arg
            325   330   335

Arg Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala His
            340   345   350

Leu Gln Leu Ala Pro Ser Phe Gly Gly Leu Val Ser Leu Glu Lys Leu
        355   360   365

Asp Met His Gly Ile Phe Phe Arg Ser Leu Thr Asn Thr Thr Leu Arg
    370   375   380

Pro Leu Thr Gln Leu Pro Lys Leu Gln Ser Leu Ser Leu Gln Leu Asn
385   390   395   400

Phe Ile Asn Gln Ala Glu Leu Ser Ile Phe Gly Ala Phe Pro Ser Leu
            405   410   415

Leu Phe Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ala Arg Pro
            420   425   430

Val Ala Ala Leu Gly Glu Val Asp Ser Gly Val Glu Val Trp Arg Trp
        435   440   445

Pro Arg Gly Leu Ala Pro Gly Pro Leu Ala Ala Val Ser Ala Lys Asp
    450   455   460

Phe Met Pro Ser Cys Asn Leu Asn Phe Thr Leu Asp Leu Ser Arg Asn
465   .   470   475   480

Asn Leu Val Thr Ile Gln Gln Glu Met Phe Thr Arg Leu Ser Arg Leu
                485   490   495

Gln Cys Leu Arg Leu Ser His Asn Ser Ile Ser Gln Ala Val Asn Gly
          500   505   510

Ser Gln Phe Val Pro Leu Thr Arg Leu Arg Val Leu Asp Leu Ser Tyr
          515   520   525

Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr Glu Leu Pro Gln
     530   535   540

Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Ser Met Gln
545   550   555   560

Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu Pro Ser Leu Arg
               565   570   575

Tyr Leu Ser Leu Ala His Asn Gly Ile His Ser Arg Val Ser Gln Lys
          580   585   590

Leu Ser Ser Ala Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn Ser Leu
          595   600   605

Ser Gln Met Trp Ala Glu Gly Asp Leu Tyr Leu Cys Phe Phe Lys Gly
     610   615   620

Leu Arg Asn Leu Val Gln Leu Asp Leu Ser Lys Asn His Leu His Thr
625   630   635   640

Leu Leu Pro Arg His Leu Asp Asn Leu Pro Lys Ser Leu Arg Gln Leu
               645   650   655

Arg Leu Arg Asp Asn Asn Leu Ala Phe Phe Asn Trp Ser Ser Leu Thr
          660   665   670

Val Leu Pro Gln Leu Glu Ala Leu Asp Leu Ala Gly Asn Gln Leu Lys
          675   680   685

Ala Leu Ser Asn Gly Ser Leu Pro Pro Gly Thr Arg Leu Gln Lys Leu
     690   695   700

Asp Val Ser Ser Asn Ser Ile Gly Phe Val Thr Pro Gly Phe Phe Val
705   710   715   720

Leu Ala Asn Arg Leu Lys Glu Leu Asn Leu Ser Ala Asn Ala Leu Lys
                  725   730   735

Thr Val Asp Pro Phe Trp Phe Gly Arg Leu Thr Glu Thr Leu Asn Ile
              740   745   750

Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala Ala Phe
          755   760   765

Val Asp Phe Leu Leu Glu Met Gln Ala Ala Val Pro Gly Leu Ser Arg
        770   775   780

Arg Val Thr Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg Ser Ile Phe
785   790   795   800

Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Thr Leu Ser Leu Asp Cys
              805   810   815

Phe Gly Phe Ser Leu Leu Met Val Ala Leu Gly Leu Ala Val Pro Met
          820   825   830

Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His Leu Cys
          835   840   845

Leu Ala His Leu Pro Arg Arg Arg Arg Gln Arg Gly Glu Asp Thr Leu
850   855   860

Leu Tyr Asp Ala Phe Val Val Phe Asp Lys Ala Gln Ser Ala Val Ala
865   870   875   880

Asp Trp Val Tyr Asn Glu Leu Arg Val Gln Leu Glu Glu Arg Arg Gly
              885   890   895

Arg Arg Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp Trp Leu Pro Gly
          900   905   910

Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr Ser Ser Arg Lys
          915   920   925

Thr Met Phe Val Leu Asp His Thr Asp Arg Val Ser Gly Leu Leu Arg

             930   935   940

Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu Asp Arg Lys Asp
945   950   955   960

Val Val Val Leu Val Ile Leu Arg Pro Ala Ala Tyr Arg Ser Arg Tyr
                965   970   975

Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val Leu Leu Trp Pro
             980   985   990

His Gln Pro Ser Gly Gln Gly Ser Phe Trp Ala Asn Leu Gly Met Ala
         995   1000   1005

Leu Thr Arg Asp Asn Arg His Phe Tyr Asn Arg Asn Phe Cys Arg
    1010   1015   1020

Gly Pro Thr Thr Ala Glu
    1025

<210> 18
<211> 818
<212> PRT
<213> Ovis aries

<400> 18

Met Gly Pro Tyr Cys Ala Pro His Pro Leu Ser Leu Leu Val Gln Ala
1   5   10   15

Ala Ala Leu Ala Ala Ala Leu Ala Gln Gly Thr Leu Pro Ala Phe Leu
            20   25   30

Pro Cys Glu Leu Gln Pro Arg Gly Lys Val Asn Cys Asn Trp Leu Phe
        35   40   45

Leu Lys Ser Val Pro Arg Phe Ser Ala Gly Ala Pro Arg Ala Asn Val
    50   55   60

Thr Ser Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asp Ser
65   70   75   80

Asp Phe Val His Leu Ser Asn Leu Arg Val Leu Asn Leu Lys Trp Asn
            85   90   95

Cys Pro Pro Ala Gly Leu Ser Pro Met His Phe Pro Cys Arg Met Thr

```
                    100                     105              `  110

      Ile Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu Asn
          115                 120             125

      Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Ala Leu Pro Ser Ser Leu
          130                 135             140

      Val Ser Leu Ser Leu Ser Arg Thr Ser Ile Leu Val Leu Gly Pro Thr
      145                 150             155                 160

      His Phe Thr Gly Leu His Ala Leu Arg Phe Leu Tyr Met Asp Gly Asn
                      165                 170             175

      Cys Tyr Tyr Lys Asn Pro Cys Gln Gln Ala Val Glu Val Ala Pro Gly
                  180                 185             190

      Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr Asn
                  195                 200             205

      Asn Leu Thr Glu Val Pro Arg Arg Leu Pro Pro Ser Leu Asp Thr Leu
          210                 215             220

      Leu Leu Ser Tyr Asn His Ile Ile Thr Leu Ala Pro Glu Asp Leu Ala
      225                 230             235                 240

      Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg Arg
                      245                 250             255

      Cys Asp His Ala Arg Asn Pro Cys Arg Glu Cys Pro Lys Asn Phe Pro
                  260                 265             270

      Lys Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly Leu
                  275                 280             285

      Val Leu Lys Asp Ser Ser Leu Tyr Lys Leu Glu Lys Asp Trp Phe Arg
          290                 295             300

      Gly Leu Gly Arg Leu Gln Val Leu Asp Leu Ser Glu Asn Phe Leu Tyr
      305                 310             315                 320

      Asp Tyr Ile Thr Lys Thr Thr Ile Phe Arg Asn Leu Thr Gln Leu Arg
                      325                 330             335
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Arg Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala His
　　　　　340　　　　　　　　　345　　　　　　　　　350

Leu Gln Leu Ala Pro Ser Phe Gly Gly Leu Val Ser Leu Glu Lys Leu
　　　355　　　　　　　　360　　　　　　　　365

Asp Met His Gly Ile Phe Phe Arg Ser Leu Thr Asn Thr Thr Leu Arg
　　370　　　　　　　　375　　　　　　　　380

Pro Leu Thr Gln Leu Pro Lys Leu Gln Ser Leu Ser Leu Gln Leu Asn
385　　　　　　　　390　　　　　　　　395　　　　　　　　400

Phe Ile Asn Gln Ala Glu Leu Ser Ile Phe Gly Ala Phe Pro Ser Leu
　　　　　405　　　　　　　　410　　　　　　　　415

Leu Phe Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ala Arg Pro
　　　　　420　　　　　　　　425　　　　　　　　430

Val Ala Ala Leu Gly Glu Val Asp Ser Gly Val Glu Val Trp Arg Trp
　　　435　　　　　　　　440　　　　　　　　445

Pro Arg Gly Leu Ala Pro Gly Pro Leu Ala Ala Val Ser Ala Lys Asp
　　　450　　　　　　　　455　　　　　　　　460

Phe Met Pro Ser Cys Asn Leu Asn Phe Thr Leu Asp Leu Ser Arg Asn
465　　　　　　　　470　　　　　　　　475　　　　　　　　480

Asn Leu Val Thr Ile Gln Gln Glu Met Phe Thr Arg Leu Ser Arg Leu
　　　　　485　　　　　　　　490　　　　　　　　495

Gln Cys Leu Arg Leu Ser His Asn Ser Ile Ser Gln Ala Val Asn Gly
　　　　　500　　　　　　　　505　　　　　　　　510

Ser Gln Phe Val Pro Leu Thr Arg Leu Arg Val Leu Asp Leu Ser Tyr
　　　515　　　　　　　　520　　　　　　　　525

Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr Glu Leu Pro Gln
　　　530　　　　　　　　535　　　　　　　　540

Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Ser Met Gln
545　　　　　　　　550　　　　　　　　555　　　　　　　　560

Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu Pro Ser Leu Arg
　　　　　565　　　　　　　　570　　　　　　　　575

```
Tyr Leu Ser Leu Ala His Asn Gly Ile His Ser Arg Val Ser Gln Lys
        580             585             590


Leu Ser Ser Ala Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn Ser Leu
        595             600             605


Ser Gln Met Trp Ala Glu Gly Asp Leu Tyr Leu Cys Phe Phe Lys Gly
    610             615             620


Leu Arg Asn Leu Val Gln Leu Asp Leu Ser Lys Asn His Leu His Thr
625             630             635             640


Leu Leu Pro Arg His Leu Asp Asn Leu Pro Lys Ser Leu Arg Gln Leu
            645             650             655


Arg Leu Arg Asp Asn Asn Leu Ala Phe Phe Asn Trp Ser Ser Leu Thr
            660             665             670


Val Leu Pro Gln Leu Glu Ala Leu Asp Leu Ala Gly Asn Gln Leu Lys
        675             680             685


Ala Leu Ser Asn Gly Ser Leu Pro Pro Gly Thr Arg Leu Gln Lys Leu
    690             695             700


Asp Val Ser Ser Asn Ser Ile Gly Phe Val Thr Pro Gly Phe Phe Val
705             710             715             720


Leu Ala Asn Arg Leu Lys Glu Leu Asn Leu Ser Ala Asn Ala Leu Lys
            725             730             735


Thr Val Asp Pro Phe Trp Phe Gly Arg Leu Thr Glu Thr Leu Asn Ile
            740             745             750


Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala Ala Phe
        755             760             765


Val Asp Phe Leu Leu Glu Met Gln Ala Ala Val Pro Gly Leu Ser Arg
    770             775             780


Arg Val Thr Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg Ser Ile Phe
785             790             795             800


Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Thr Leu Ser Leu Asp Cys
            805             810             815
```

Phe Gly

<210> 19
<211> 3199
<212> DNA
<213> Ovis aries

<400> 19
gtcggcacgg gaagtgagcg ccaagcatcc ttccctgcag ctgccgccca acttgcccgc   60

cagaccctct ggagaagccg cattccctgc catgggcccc tactgtgccc cgcacccct   120

ttctctcctg gtgcaggcgg cggcgctggc agcagccctg gcccagggca ccctgcctgc   180

cttcctgccc tgtgagctcc agccccgggg taaggtgaac tgcaactggc tgttcctgaa   240

gtctgtgccg cgcttttcgg ccggagcccc ccgggccaat gtcaccagcc tctccttaat   300

ctccaaccgc atccaccact gcacgactc tgacttcgtc cacctgtcca acctgcgggt   360

cctcaacctc aagtggaact gcccgccggc cggcctcagc cccatgcact cccctgccg   420

catgaccatc gagcccaaca ccttcctggc tgtgcccacc ctggaggagc tgaacctgag   480

ctacaatggc atcacgaccg tgcctgccct gcccagttct ctcgtatccc tgtcgctgag   540

ccgcaccagc atcctggtgc taggccccac ccacttcacc ggcctgcacg ccctgcgctt   600

tctgtacatg gacggcaact gctactataa gaaccccctgc cagcaggccg tggaggtggc   660

cccaggcgcc ctccttggcc tgggcaacct cacgcacctg tcgctcaagt acaacaacct   720

cacggaggtg ccccgccgcc tgccccccag cctggacacc ctgctgctgt cctacaacca   780

catcatcacc ctggcacccg aggacctggc caatctgact gccctgcgtg tgcttgatgt   840

gggcgggaac tgccgccgct gcgaccacgc ccgcaacccc tgcagggagt gcccaaagaa   900

cttccccaag ctgcaccctg acaccttcag ccacctgagc cgcctcgaag gcctggtgtt   960

gaaggacagt tctctctaca actagagaa agactggttc cgcggcctgg gcaggctcca   1020

agtgctcgac ctgagtgaga acttcctcta tgactacatc accaagacca ccatcttcag   1080

gaacctgacc cagctgcgca gactcaacct gtccttcaat taccacaaga aggtgtcctt   1140

cgcccacctg caactggcac cctcctttgg gggcctggtg tccctggaga agctggacat   1200

gcacggcatc ttcttccgct ccctcaccaa caccacgctc cggccgctga cccagctgcc   1260

caagctccag agtctgagtc tgcagctgaa cttcatcaac caggccgagc tcagcatctt   1320

tgggggccttc ccgagcctgc tcttcgtgga cctgtcggac aaccgcatca gcggagctgc   1380

gaggccggtg gccgccctcg gggaggtgga cagcagcgtg gaagtctggc ggtggcccag   1440

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gggcctcgct ccaggcccgc tggccgccgt cagcgcaaag gacttcatgc caagctgcaa    1500

cctcaacttc accttggacc tgtcacggaa caacctggtg acgatccagc aggagatgtt    1560

tacccgcctc tcccgcctcc agtgcctgcg cctgagccac aacagcatct cgcaggcggt    1620

taatggctcg cagttcgtgc cgctgacccg cctgcgagtg ctcgacctgt cctacaacaa    1680

gctggacctg taccatgggc gctcgttcac ggagctgccg cagctggagg cactggacct    1740

cagctacaac agccagccct tcagcatgca gggcgtgggc cacaacctca gcttcgtggc    1800

ccagctgccg tccctgcgct acctcagcct tgcgcacaac ggcatccaca gccgcgtgtc    1860

acagaagctc agcagcgcct cgctgcgcgc cctggacttc agcggcaact ccctgagcca    1920

gatgtgggcc gagggagacc tctatctctg cttcttcaaa ggcttgagga acctggtcca    1980

gctggacctg tccaagaacc acctgcacac cctcctgcct cgtcacctgg ataacctgcc    2040

caagagcctg cggcagctgc gtctccggga caataacctg gccttcttca actggagcag    2100

cctgactgtt ctgccccagc tggaagccct ggatctggcg ggaaaccagc tgaaggccct    2160

gagcaacggc agcctgccac ctggcacccg gctccagaag ctggacgtga gcagcaacag    2220

catcggcttt gtgacccctg gcttctttgt ccttgccaac cggctgaaag agcttaacct    2280

cagcgccaac gccctgaaga cagtggatcc cttctggttc ggtcgcttaa cagagaccct    2340

gaatatccta gacgtgagcg ccaacccgct ccactgtgcc tgcggggcgg cctttgtgga    2400

cttcctgctg gagatgcagg cggccgtgcc tgggctgtcc aggcgcgtca cgtgtggcag    2460

tccgggccag ctccagggcc gcagcatctt cgcacaggac ctgcgcctct gcctggatga    2520

gaccctctcc ttggactgct ttggcttctc gctgctaatg gtggcgctgg gcctggcggt    2580

gcccatgctg caccacctct gtggctggga cctgtggtac tgcttccacc tgtgtctggc    2640

ccatttgccc cgacggcggc ggcagcgggg cgaggacacc ctgctctacg atgccttcgt    2700

ggtcttcgac aaggcgcaga gtgcagtggc cgactgggtg tacaacgagc tccgcgtgca    2760

gctggaggag cgccgcgggc gccgggcgct ccgcctctgc ctggaggagc gagactggct    2820

ccctggcaag acgctcttcg agaacctgtg ggcctcggtc tacagcagcc gtaagaccat    2880

gttcgtgctg gaccacacgg accgggtcag tggcctcctg cgcgccagct tcctgctggc    2940

ccagcagcgc ctgttggagg accgcaagga tgtcgtggtg ctggtgatcc tgcgccccgc    3000

cgcctaccgg tcccgctacg tgcggctgcg ccagcgcctc tgccgccaga gcgtcctcct    3060

ctggccccac cagcccagtg gccagggtag cttctgggcc aacctgggca tggccctgac    3120

cagggacaac cgccacttct ataaccggaa cttctgccgg ggccccacga cagccgaata    3180
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gcacagagtg actgcccag                                                  3199


<210>  20
<211>  2454
<212>  DNA
<213>  Ovis aries

<400>  20
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aaggtgaact gcaactggct gttcctgaag tctgtgccgc gcttttcggc cggagccccc     180

cgggccaatg tcaccagcct ctccttaatc tccaaccgca tccaccactt gcacgactct     240

gacttcgtcc acctgtccaa cctgcgggtc ctcaacctca agtggaactg cccgccggcc     300

ggcctcagcc ccatgcactt cccctgccgc atgaccatcg agcccaacac cttcctggct     360

gtgcccaccc tggaggagct gaacctgagc tacaatggca tcacgaccgt gcctgccctg     420

cccagttctc tcgtatccct gtcgctgagc cgcaccagca tcctggtgct aggccccacc     480

cacttcaccg gcctgcacgc cctgcgcttt ctgtacatgg acggcaactg ctactataag     540

aaccccctgcc agcaggccgt ggaggtggcc ccaggcgccc tccttggcct gggcaacctc     600

acgcacctgt cgctcaagta caacaacctc acggaggtgc cccgccgcct gcccccccagc     660

ctggacaccc tgctgctgtc ctacaaccac atcatcaccc tggcacccga ggacctggcc     720

aatctgactg ccctgcgtgt gcttgatgtg ggcgggaact gccgccgctg cgaccacgcc     780

cgcaacccct gcagggagtg cccaaagaac ttccccaagc tgcaccctga caccttcagc     840

cacctgagcc gcctcgaagg cctggtgttg aaggacagtt ctctctacaa actagagaaa     900

gactggttcc gcggcctggg caggctccaa gtgctcgacc tgagtgagaa cttcctctat     960

gactacatca ccaagaccac catcttcagg aacctgaccc agctgcgcag actcaacctg    1020

tccttcaatt accacaagaa ggtgtccttc gcccacctgc aactggcacc ctcctttggg    1080

ggcctggtgt ccctggagaa gctggacatg cacggcatct tcttccgctc cctcaccaac    1140

accacgctcc ggccgctgac ccagctgccc aagctccaga gtctgagtct gcagctgaac    1200

ttcatcaacc aggccgagct cagcatcttt ggggccttcc cgagcctgct cttcgtggac    1260

ctgtcggaca accgcatcag cggagctgcg aggccggtgg ccgccctcgg ggaggtggac    1320

agcgggggtgg aagtctggcg gtggcccagg ggcctcgctc caggcccgct ggccgccgtc    1380

agcgcaaagg acttcatgcc aagctgcaac ctcaacttca ccttggacct gtcacggaac    1440

aacctggtga cgatccagca ggagatgttt acccgcctct cccgcctcca gtgcctgcgc    1500
```

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ctgagccaca acagcatctc gcaggcggtt aatggctcgc agttcgtgcc gctgacccgc   1560

ctgcgagtgc tcgacctgtc ctacaacaag ctggacctgt accatgggcg ctcgttcacg   1620

gagctgccgc agctggaggc actggacctc agctacaaca gccagccctt cagcatgcag   1680

ggcgtgggcc acaacctcag cttcgtggcc cagctgccgt ccctgcgcta cctcagcctt   1740

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ctggacttca gcggcaactc cctgagccag atgtgggccg agggagacct ctatctctgc   1860

ttcttcaaag gcttgaggaa cctggtccag ctggacctgt ccaagaacca cctgcacacc   1920

ctcctgcctc gtcacctgga taacctgccc aagagcctgc ggcagctgcg tctccgggac   1980

aataacctgg ccttcttcaa ctggagcagc ctgactgttc tgccccagct ggaagccctg   2040

gatctggcgg gaaaccagct gaaggccctg agcaacggca gcctgccacc tggcacccgg   2100

ctccagaagc tggacgtgag cagcaacagc atcggctttg tgacccctgg cttctttgtc   2160

cttgccaacc ggctgaaaga gcttaacctc agcgccaacg ccctgaagac agtggatccc   2220

ttctggttcg gtcgcttaac agagaccctg aatatcctag acgtgagcgc caacccgctc   2280

cactgtgcct gcggggcggc ctttgtggac ttcctgctgg agatgcaggc ggccgtgcct   2340

gggctgtcca ggcgcgtcac gtgtggcagt ccgggccagc tccagggccg cagcatcttc   2400

gcacaggacc tgcgcctctg cctggatgag accctctcct ggactgctt tggc         2454
```

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<210>  21
<211>  1032
<212>  PRT
<213>  Canis familiaris

<400>  21

Met Gly Pro Cys Arg Gly Ala Leu His Pro Leu Ser Leu Leu Val Gln
1               5                   10                  15


Ala Ala Ala Leu Ala Leu Ala Leu Ala Gln Gly Thr Leu Pro Ala Phe
            20                  25                  30


Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu
        35                  40                  45


Phe Leu Lys Ser Val Pro Arg Phe Ser Ala Ala Ala Pro Arg Gly Asn
    50                  55                  60


Val Thr Ser Leu Ser Leu Tyr Ser Asn Arg Ile His His Leu His Asp
65                  70                  75                  80
```

```
Tyr Asp Phe Val His Phe Val His Leu Arg Arg Leu Asn Leu Lys Trp
                85              90              95

Asn Cys Pro Pro Ala Ser Leu Ser Pro Met His Phe Pro Cys His Met
            100             105             110

Thr Ile Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Asp Leu
        115             120             125

Asn Leu Ser Tyr Asn Ser Ile Thr Thr Val Pro Ala Leu Pro Ser Ser
    130             135             140

Leu Val Ser Leu Ser Leu Ser Arg Thr Asn Ile Leu Val Leu Asp Pro
145             150             155             160

Ala Thr Leu Ala Gly Leu Tyr Ala Leu Arg Phe Leu Phe Leu Asp Gly
                165             170             175

Asn Cys Tyr Tyr Lys Asn Pro Cys Gln Gln Ala Leu Gln Val Ala Pro
            180             185             190

Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr
        195             200             205

Asn Asn Leu Thr Val Val Pro Arg Gly Leu Pro Pro Ser Leu Glu Tyr
    210             215             220

Leu Leu Leu Ser Tyr Asn His Ile Ile Thr Leu Ala Pro Glu Asp Leu
225             230             235             240

Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
            245             250             255

Arg Cys Asp His Ala Arg Asn Pro Cys Arg Glu Cys Pro Lys Gly Phe
            260             265             270

Pro Gln Leu His Pro Asn Thr Phe Gly His Leu Ser His Leu Glu Gly
        275             280             285

Leu Val Leu Arg Asp Ser Ser Leu Tyr Ser Leu Asp Pro Arg Trp Phe
    290             295             300

His Gly Leu Gly Asn Leu Met Val Leu Asp Leu Ser Glu Asn Phe Leu
305             310             315             320
```

Tyr Asp Cys Ile Thr Lys Thr Lys Ala Phe Tyr Gly Leu Ala Arg Leu
                325   330   335

Arg Arg Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala
            340   345   350

His Leu His Leu Ala Ser Ser Phe Gly Ser Leu Leu Ser Leu Gln Glu
        355   360   365

Leu Asp Ile His Gly Ile Phe Phe Arg Ser Leu Ser Lys Thr Thr Leu
    370   375   380

Gln Ser Leu Ala His Leu Pro Met Leu Gln Arg Leu His Leu Gln Leu
385   390   395   400

Asn Phe Ile Ser Gln Ala Gln Leu Ser Ile Phe Gly Ala Phe Pro Gly
            405   410   415

Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ala Glu
        420   425   430

Pro Ala Ala Ala Thr Gly Glu Val Glu Ala Asp Cys Gly Glu Arg Val
    435   440   445

Trp Pro Gln Ser Arg Asp Leu Ala Leu Gly Pro Leu Gly Thr Pro Gly
    450   455   460

Ser Glu Ala Phe Met Pro Ser Cys Arg Thr Leu Asn Phe Thr Leu Asp
465   470   475   480

Leu Ser Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Val Arg
            485   490   495

Leu Ala Arg Leu Gln Cys Leu Gly Leu Ser His Asn Ser Ile Ser Gln
        500   505   510

Ala Val Asn Gly Ser Gln Phe Val Pro Leu Ser Asn Leu Arg Val Leu
        515   520   525

Asp Leu Ser His Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr
    530   535   540

Glu Leu Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro

- 61 -

545   550 ·   555   560

Phe Ser Met Arg Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu
                    565   570   575

Pro Ala Leu Arg Tyr Leu Ser Leu Ala His Asn Gly Ile His Ser Arg
            580   585   590

Val Ser Gln Gln Leu Arg Ser Ala Ser Leu Arg Ala Leu Asp Phe Ser
        595   600   605

Gly Asn Thr Leu Ser Gln Met Trp Ala Glu Gly Asp Leu Tyr Leu Arg
    610   615   620

Phe Phe Gln Gly Leu Arg Ser Leu Val Gln Leu Asp Leu Ser Gln Asn
625   630   635   640

Arg Leu His Thr Leu Leu Pro Arg Asn Leu Asp Asn Leu Pro Lys Ser
                645   650   655

Leu Arg Leu Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Asn Trp
            660   665   670

Ser Ser Leu Ala Leu Leu Pro Lys Leu Glu Ala Leu Asp Leu Ala Gly
            675   680   685

Asn Gln Leu Lys Ala Leu Ser Asn Gly Ser Leu Pro Asn Gly Thr Gln
    690   695   700

Leu Gln Arg Leu Asp Leu Ser Gly Asn Ser Ile Gly Phe Val Val Pro
705   710   715   720

Ser Phe Phe Ala Leu Ala Val Arg Leu Arg Glu Leu Asn Leu Ser Ala
            725   730   735

Asn Ala Leu Lys Thr Val Glu Pro Ser Trp Phe Gly Ser Leu Ala Gly
            740   745   750

Ala Leu Lys Val Leu Asp Val Thr Ala Asn Pro Leu His Cys Ala Cys
            755   760   765

Gly Ala Thr Phe Val Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro
    770   775   780

Gly Leu Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly
785   790   795   800

Arg Ser Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu
            805   810   815

Ser Trp Val Cys Phe Ser Leu Ser Leu Leu Ala Val Ala Leu Ser Leu
            820   825   830

Ala Val Pro Met Leu His Gln Leu Cys Gly Trp Asp Leu Trp Tyr Cys
            835   840   845

Phe His Leu Cys Leu Ala Trp Leu Pro Arg Arg Gly Arg Arg Arg Gly
    850   855   860

Val Asp Ala Leu Ala Tyr Asp Ala Phe Val Val Phe Asp Lys Ala Gln
865   870   875   880

Ser Ser Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Val Gln Leu Glu
            885   890   895

Glu Arg Arg Gly Arg Arg Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp
            900   905   910

Trp Val Pro Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr
            915   920   925

Ser Ser Arg Lys Thr Leu Phe Val Leu Ala Arg Thr Asp Arg Val Ser
    930   935   940

Gly Leu Leu Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu
945   950   955   960

Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Cys Pro Asp Ala His
            965   970   975

Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val
            980   985   990

Leu Leu Trp Pro His Gln Pro Ser Gly Gln Arg Ser Phe Trp Ala Gln
        995   1000   1005

Leu Gly Thr Ala Leu Thr Arg Asp Asn Arg His Phe Tyr Asn Gln
    1010   1015   1020

- 63 -

```
Asn Phe  Cys Arg Gly Pro Thr  Thr Ala
    1025                 1030
```

```
<210>  22
<211>  822
<212>  PRT
<213>  Canis familiaris
```

```
<400>  22
```

```
Met Gly Pro Cys Arg Gly Ala Leu His Pro Leu Ser Leu Leu Val Gln
1               5                   10              15
```

```
Ala Ala Ala Leu Ala Leu Ala Leu Ala Gln Gly Thr Leu Pro Ala Phe
            20              25              30
```

```
Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu
        35              40              45
```

```
Phe Leu Lys Ser Val Pro Arg Phe Ser Ala Ala Ala Pro Arg Gly Asn
    50              55              60
```

```
Val Thr Ser Leu Ser Leu Tyr Ser Asn Arg Ile His His Leu His Asp
65              70              75              80
```

```
Tyr Asp Phe Val His Phe Val His Leu Arg Arg Leu Asn Leu Lys Trp
            85              90              95
```

```
Asn Cys Pro Pro Ala Ser Leu Ser Pro Met His Phe Pro Cys His Met
            100             105             110
```

```
Thr Ile Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Asp Leu
        115             120             125
```

```
Asn Leu Ser Tyr Asn Ser Ile Thr Thr Val Pro Ala Leu Pro Ser Ser
    130             135             140
```

```
Leu Val Ser Leu Ser Leu Ser Arg Thr Asn Ile Leu Val Leu Asp Pro
145             150             155             160
```

```
Ala Thr Leu Ala Gly Leu Tyr Ala Leu Arg Phe Leu Phe Leu Asp Gly
            165             170             175
```

```
Asn Cys Tyr Tyr Lys Asn Pro Cys Gln Gln Ala Leu Gln Val Ala Pro
            180             185             190
```

Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr
        195   200   205

Asn Asn Leu Thr Val Val Pro Arg Gly Leu Pro Pro Ser Leu Glu Tyr
    210   215   220

Leu Leu Leu Ser Tyr Asn His Ile Ile Thr Leu Ala Pro Glu Asp Leu
225   230   235   240

Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
            245   250   255

Arg Cys Asp His Ala Arg Asn Pro Cys Arg Glu Cys Pro Lys Gly Phe
            260   ,   265   270

Pro Gln Leu His Pro Asn Thr Phe Gly His Leu Ser His Leu Glu Gly
        275   280   .   285

Leu Val Leu Arg Asp Ser Ser Leu Tyr Ser Leu Asp Pro Arg Trp Phe
        290   295   300

His Gly Leu Gly Asn Leu Met Val Leu Asp Leu Ser Glu Asn Phe Leu
305   310   315   320

Tyr Asp Cys Ile Thr Lys Thr Lys Ala Phe Tyr Gly Leu Ala Arg Leu
            325   330   335

Arg Arg Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala
            340   345   350

His Leu His Leu Ala Ser Ser Phe Gly Ser Leu Leu Ser Leu Gln Glu
        355   360   365

Leu Asp Ile His Gly Ile Phe Phe Arg Ser Leu Ser Lys Thr Thr Leu
    370   375   380

Gln Ser Leu Ala His Leu Pro Met Leu Gln Arg Leu His Leu Gln Leu
385   390   395   400

Asn Phe Ile Ser Gln Ala Gln Leu Ser Ile Phe Gly Ala Phe Pro Gly
            405   410   415

Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ala Glu
        420   425   430

Pro Ala Ala Ala Thr Gly Glu Val Glu Ala Asp Cys Gly Glu Arg Val
        435   440   445

Trp Pro Gln Ser Arg Asp Leu Ala Leu Gly Pro Leu Gly Thr Pro Gly
    450   455   460

Ser Glu Ala Phe Met Pro Ser Cys Arg Thr Leu Asn Phe Thr Leu Asp
465   470   475   480

Leu Ser Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Val Arg
            485   490   495

Leu Ala Arg Leu Gln Cys Leu Gly Leu Ser His Asn Ser Ile Ser Gln
        500   505   510

Ala Val Asn Gly Ser Gln Phe Val Pro Leu Ser Asn Leu Arg Val Leu
        515   520   525

Asp Leu Ser His Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr
    530   535   540

Glu Leu Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro
545   550   555   560

Phe Ser Met Arg Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu
            565   570   575

Pro Ala Leu Arg Tyr Leu Ser Leu Ala His Asn Gly Ile His Ser Arg
        580   585   590

Val Ser Gln Gln Leu Arg Ser Ala Ser Leu Arg Ala Leu Asp Phe Ser
    595   600   605

Gly Asn Thr Leu Ser Gln Met Trp Ala Glu Gly Asp Leu Tyr Leu Arg
    610   615   620

Phe Phe Gln Gly Leu Arg Ser Leu Val Gln Leu Asp Leu Ser Gln Asn
625   630   635   640

Arg Leu His Thr Leu Leu Pro Arg Asn Leu Asp Asn Leu Pro Lys Ser
            645   650   655

Leu Arg Leu Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Asn Trp

-66-

```
                     660                     665                     670
```

Ser Ser Leu Ala Leu Leu Pro Lys Leu Glu Ala Leu Asp Leu Ala Gly
        675   680   685

Asn Gln Leu Lys Ala Leu Ser Asn Gly Ser Leu Pro Asn Gly Thr Gln
        690   695   700

Leu Gln Arg Leu Asp Leu Ser Gly Asn Ser Ile Gly Phe Val Val Pro
705   710   715   720

Ser Phe Phe Ala Leu Ala Val Arg Leu Arg Glu Leu Asn Leu Ser Ala
            725   730   735

Asn Ala Leu Lys Thr Val Glu Pro Ser Trp Phe Gly Ser Leu Ala Gly
            740   745   750

Ala Leu Lys Val Leu Asp Val Thr Ala Asn Pro Leu His Cys Ala Cys
        755   760   765

Gly Ala Thr Phe Val Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro
    770   775   780

Gly Leu Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly
785   790   795   800

Arg Ser Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu
            805   810   815

Ser Trp Val Cys Phe Ser
            820

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<210>   23
<211>   3334
<212>   DNA
<213>   Canis familiaris

<400>   23
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ctgtctctcc tggtgcaggc tgccgcgcta gccctggccc tggcccaggg caccctgcct    180

gccttcctgc cctgtgagct ccagccccat ggcctggtga actgcaactg gctgttcctc    240

aagtccgtgc cccgcttctc ggcagctgca ccccgcggta acgtcaccag cctttccttg    300
```

```
tactccaacc gcatccacca cctccatgac tatgactttg tccacttcgt ccacctgcgg    360

cgtctcaatc tcaagtggaa ctgcccgccc gccagcctca gccccatgca ctttccctgt    420

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<213>   Canis familiaris

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ggcctggtga actgcaactg gctgttcctc aagtccgtgc ccgcttctc ggcagctgca   180

ccccgcggta acgtcaccag cctttccttg tactccaacc gcatccacca cctccatgac   240

tatgactttg tccacttcgt ccacctgcgg cgtctcaatc tcaagtggaa ctgcccgccc   300
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cgcctgcata ccctcctgcc acgcaacctg gacaacctcc caagagcct gcggctcctg   1980

cggctccgtg acaattacct ggctttcttc aactggagca gcctggccct cctacccaag   2040
```

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gccaacccct tgcattgcgc ttgcggcgca accttcgtgg acttcttgct ggaggtgcag    2340

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<211> 1031
<212> PRT
<213> Felis catus

<400> 25

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Ala Ala Ala Leu Ala Val Ala Leu Ala Gln Gly Thr Leu Pro Ala Phe
            20                  25                  30


Leu Pro Cys Glu Leu Gln Arg His Gly Leu Val Asn Cys Asp Trp Leu
        35                  40                  45


Phe Leu Lys Ser Val Pro His Phe Ser Ala Ala Ala Pro Arg Gly Asn
    50                  55                  60


Val Thr Ser Leu Ser Leu Tyr Ser Asn Arg Ile His His Leu His Asp
65                  70                  75                  80


Ser Asp Phe Val His Leu Ser Ser Leu Arg Arg Leu Asn Leu Lys Trp
                85                  90                  95


Asn Cys Pro Pro Ala Ser Leu Ser Pro Met His Phe Pro Cys His Met
                100                 105                 110


Thr Ile Glu Pro His Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu
            115                 120                 125


Asn Leu Ser Tyr Asn Ser Ile Thr Thr Val Pro Ala Leu Pro Ser Ser
        130                 135                 140
```

```
Leu Val Ser Leu Ser Leu Ser Arg Thr Asn Ile Leu Val Leu Asp Pro
145                 150                 155                 160

Ala Asn Leu Ala Gly Leu His Ser Leu Arg Phe Leu Phe Leu Asp Gly
                165                 170                 175

Asn Cys Tyr Tyr Lys Asn Pro Cys Pro Gln Ala Leu Gln Val Ala Pro
            180                 185                 190

Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr
        195                 200                 205

Asn Asn Leu Thr Ala Val Pro Arg Gly Leu Pro Pro Ser Leu Glu Tyr
210                 215                 220

Leu Leu Leu Ser Tyr Asn His Ile Ile Thr Leu Ala Pro Glu Asp Leu
225                 230                 235                 240

Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
                245                 250                 255

Arg Cys Asp His Ala Arg Asn Pro Cys Met Glu Cys Pro Lys Gly Phe
            260                 265                 270

Pro His Leu His Pro Asp Thr Phe Ser His Leu Asn His Leu Glu Gly
        275                 280                 285

Leu Val Leu Lys Asp Ser Ser Leu Tyr Asn Leu Asn Pro Arg Trp Phe
    290                 295                 300

His Ala Leu Gly Asn Leu Met Val Leu Asp Leu Ser Glu Asn Phe Leu
305                 310                 315                 320

Tyr Asp Cys Ile Thr Lys Thr Thr Ala Phe Gln Gly Leu Ala Gln Leu
            325                 330                 335

Arg Arg Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala
        340                 345                 350

His Leu His Leu Ala Pro Ser Phe Gly Ser Leu Leu Ser Leu Gln Gln
        355                 360                 365

Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Ser Glu Thr Thr Leu
370                 375                 380
```

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Arg Ser Leu Val His Leu Pro Met Leu Gln Ser Leu His Leu Gln Met
385   390   395   400

Asn Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Ala Phe Pro Gly
            405   410   415

Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Met Glu
            420   425   430

Leu Ala Ala Ala Thr Gly Glu Val Asp Gly Gly Glu Arg Val Arg Leu
            435   440   445

Pro Ser Gly Asp Leu Ala Leu Gly Pro Pro Gly Thr Pro Ser Ser Glu
    450   455   460

Gly Phe Met Pro Gly Cys Lys Thr Leu Asn Phe Thr Leu Asp Leu Ser
465   470   475   480

Arg Asn Asn Leu Val Thr Ile Gln Pro Glu Met Phe Ala Arg Leu Ser
            485   490   495

Arg Leu Gln Cys Leu Leu Leu Ser Arg Asn Ser Ile Ser Gln Ala Val
            500   505   510

Asn Gly Ser Gln Phe Met Pro Leu Thr Ser Leu Gln Val Leu Asp Leu
            515   520   525

Ser His Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr Glu Leu
    530   535   540

Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Ser
545   550   555   560

Met Gln Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu Pro Ala
            565   570   575

Leu Arg Tyr Leu Ser Leu Ala His Asn Asp Ile His Ser Arg Val Ser
            580   585   590

Gln Gln Leu Cys Ser Ala Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn
    595   600   605

Ala Leu Ser Arg Met Trp Ala Glu Gly Asp Leu Tyr Leu His Phe Phe

```
                610                      615                      620
```

```
Arg Gly Leu Arg Ser Leu Val Arg Leu Asp Leu Ser Gln Asn Arg Leu
625             630             635                     640
```

```
His Thr Leu Leu Pro Arg Thr Leu Asp Asn Leu Pro Lys Ser Leu Arg
                645             650             655
```

```
Leu Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Asn Trp Ser Ser
                660             665             670
```

```
Leu Val Leu Leu Pro Arg Leu Glu Ala Leu Asp Leu Ala Gly Asn Gln
            675             680             685
```

```
Leu Lys Ala Leu Ser Asn Gly Ser Leu Pro Asn Gly Thr Gln Leu Gln
        690             695             700
```

```
Arg Leu Asp Leu Ser Ser Asn Ser Ile Ser Phe Val Ala Ser Ser Phe
705             710             715             720
```

```
Phe Ala Leu Ala Thr Arg Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala
                725             730             735
```

```
Leu Lys Thr Val Glu Pro Ser Trp Phe Gly Ser Leu Ala Gly Thr Leu
            740             745             750
```

```
Lys Val Leu Asp Val Thr Gly Asn Pro Leu His Cys Ala Cys Gly Ala
        755             760             765
```

```
Ala Phe Val Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu
        770             775             780
```

```
Pro Gly His Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg Ser
785             790             795             800
```

```
Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu Ser Trp
                805             810             815
```

```
Asp Cys Phe Gly Leu Ser Leu Leu Thr Val Ala Leu Gly Leu Ala Val
            820             825             830
```

```
Pro Met Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His
            835             840             845
```

```
Leu Cys Leu Ala Trp Leu Pro Arg Arg Gly Arg Arg Gly Ala Asp
    850              855              860

Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Ala Gln Ser Ala
865              870              875              880

Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Val Arg Leu Glu Glu Arg
                885              890              895

Arg Gly Arg Arg Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp Trp Leu
        900              905              910

Pro Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr Ser Ser
        915              920              925

Arg Lys Met Leu Phe Val Leu Ala His Thr Asp Arg Val Ser Gly Leu
    930              935              940

Leu Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu Asp Arg
945              950              955              960

Lys Asp Val Val Val Leu Val Ile Leu Arg Pro Asp Ala His Arg Ser
                965              970              975

Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val Leu Leu
        980              985              990

Trp Pro His Gln Pro Ser Gly Gln Arg Ser Phe Trp Ala Gln Leu Gly
    995              1000             1005

Thr Ala Leu Thr Arg Asp Asn Gln His Phe Tyr Asn Gln Asn Phe
    1010             1015             1020

Cys Arg Gly Pro Thr Thr Ala Glu
    1025             1030

<210>   26
<211>   820
<212>   PRT
<213>   Felis catus

<400>   26

Met Gly Pro Cys His Gly Ala Leu His Pro Leu Ser Leu Leu Val Gln
1           5               10              15
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Ala Ala Ala Leu Ala Val Ala Leu Ala Gln Gly Thr Leu Pro Ala Phe
            20              25              30

Leu Pro Cys Glu Leu Gln Arg His Gly Leu Val Asn Cys Asp Trp Leu
        35              40              45

Phe Leu Lys Ser Val Pro His Phe Ser Ala Ala Ala Pro Arg Gly Asn
        50              55              60

Val Thr Ser Leu Ser Leu Tyr Ser Asn Arg Ile His His Leu His Asp
65              70              75              80

Ser Asp Phe Val His Leu Ser Ser Leu Arg Arg Leu Asn Leu Lys Trp
                85              90              95

Asn Cys Pro Pro Ala Ser Leu Ser Pro Met His Phe Pro Cys His Met
            100             105             110

Thr Ile Glu Pro His Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu
        115             120             125

Asn Leu Ser Tyr Asn Ser Ile Thr Thr Val Pro Ala Leu Pro Ser Ser
    130             135             140

Leu Val Ser Leu Ser Leu Ser Arg Thr Asn Ile Leu Val Leu Asp Pro
145             150             155             160

Ala Asn Leu Ala Gly Leu His Ser Leu Arg Phe Leu Phe Leu Asp Gly
            165             170             175

Asn Cys Tyr Tyr Lys Asn Pro Cys Pro Gln Ala Leu Gln Val Ala Pro
            180             185             190

Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr
        195             200             205

Asn Asn Leu Thr Ala Val Pro Arg Gly Leu Pro Pro Ser Leu Glu Tyr
    210             215             220

Leu Leu Leu Ser Tyr Asn His Ile Ile Thr Leu Ala Pro Glu Asp Leu
225             230             235             240

Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
            245             250             255
```

Arg Cys Asp His Ala Arg Asn Pro Cys Met Glu Cys Pro Lys Gly Phe
        260   265   270

Pro His Leu His Pro Asp Thr Phe Ser His Leu Asn His Leu Glu Gly
        275   280   285

Leu Val Leu Lys Asp Ser Ser Leu Tyr Asn Leu Asn Pro Arg Trp Phe
        290   295   300

His Ala Leu Gly Asn Leu Met Val Leu Asp Leu Ser Glu Asn Phe Leu
305   310   315   320

Tyr Asp Cys Ile Thr Lys Thr Thr Ala Phe Gln Gly Leu Ala Gln Leu
                325   330   335

Arg Arg Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala
            340   345   350

His Leu His Leu Ala Pro Ser Phe Gly Ser Leu Leu Ser Leu Gln Gln
        355   360   365

Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Ser Glu Thr Thr Leu
        370   375   380

Arg Ser Leu Val His Leu Pro Met Leu Gln Ser Leu His Leu Gln Met
385   390   395   400

Asn Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Ala Phe Pro Gly
                405   410   415

Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Met Glu
            420   425   430

Leu Ala Ala Ala Thr Gly Glu Val Asp Gly Gly Glu Arg Val Arg Leu
            435   440   445

Pro Ser Gly Asp Leu Ala Leu Gly Pro Pro Gly Thr Pro Ser Ser Glu
        450   455   460

Gly Phe Met Pro Gly Cys Lys Thr Leu Asn Phe Thr Leu Asp Leu Ser
465   470   475   480

Arg Asn Asn Leu Val Thr Ile Gln Pro Glu Met Phe Ala Arg Leu Ser
                485   490   495

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Arg Leu Gln Cys Leu Leu Leu Ser Arg Asn Ser Ile Ser Gln Ala Val
        500   505   510

Asn Gly Ser Gln Phe Met Pro Leu Thr Ser Leu Gln Val Leu Asp Leu
        515   520   525

Ser His Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr Glu Leu
        530   535   540

Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Ser
545   550   555   560

Met Gln Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu Pro Ala
                565   570   575

Leu Arg Tyr Leu Ser Leu Ala His Asn Asp Ile His Ser Arg Val Ser
            580   585   590

Gln Gln Leu Cys Ser Ala Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn
        595   600   605

Ala Leu Ser Arg Met Trp Ala Glu Gly Asp Leu Tyr Leu His Phe Phe
    610   615   620

Arg Gly Leu Arg Ser Leu Val Arg Leu Asp Leu Ser Gln Asn Arg Leu
625   630   635   640

His Thr Leu Leu Pro Arg Thr Leu Asp Asn Leu Pro Lys Ser Leu Arg
                645   650   655

Leu Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Asn Trp Ser Ser
            660   665   670

Leu Val Leu Leu Pro Arg Leu Glu Ala Leu Asp Leu Ala Gly Asn Gln
        675   680   685

Leu Lys Ala Leu Ser Asn Gly Ser Leu Pro Asn Gly Thr Gln Leu Gln
        690   695   700

Arg Leu Asp Leu Ser Ser Asn Ser Ile Ser Phe Val Ala Ser Ser Phe
705   710   715   720

Phe Ala Leu Ala Thr Arg Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala

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                  725                    730                    735
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Leu Lys Thr Val Glu Pro Ser Trp Phe Gly Ser Leu Ala Gly Thr Leu
        740   745   750

Lys Val Leu Asp Val Thr Gly Asn Pro Leu His Cys Ala Cys Gly Ala
        755   760   765

Ala Phe Val Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu
        770   775   780

Pro Gly His Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg Ser
785   790   795   800

Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu Ser Trp
                  805   810   815

Asp Cys Phe Gly
              820

<210> 27
<211> 3235
<212> DNA
<213> Felis catus

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Leu Pro Cys Glu Leu Lys Pro His Gly Leu Val Asp Cys Asn Trp Leu
        35   40   45

Phe Leu Lys Ser Val Pro Arg Phe Ser Ala Ala Ala Ser Cys Ser Asn
        50   55   60

Ile Thr Arg Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asn
65   70   75   80

Ser Asp Phe Val His Leu Ser Asn Leu Arg Gln Leu Asn Leu Lys Trp
                85   90   95

Asn Cys Pro Pro Thr Gly Leu Ser Pro Leu His Phe Ser Cys His Met
            100   105   110

Thr Ile Glu Pro Arg Thr Phe Leu Ala Met Arg Thr Leu Glu Glu Leu
        115   120   125

Asn Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Arg Leu Pro Ser Ser
        130   135   140

Leu Val Asn Leu Ser Leu Ser His Thr Asn Ile Leu Val Leu Asp Ala
145   150   155   160

Asn Ser Leu Ala Gly Leu Tyr Ser Leu Arg Val Leu Phe Met Asp Gly
            165   170   175

Asn Cys Tyr Tyr Lys Asn Pro Cys Thr Gly Ala Val Lys Val Thr Pro
            180   185   190

Gly Ala Leu Leu Gly Leu Ser Asn Leu Thr His Leu Ser Leu Lys Tyr
        195   200   205

Asn Asn Leu Thr Lys Val Pro Arg Gln Leu Pro Pro Ser Leu Glu Tyr
    210   215   220

Leu Leu Val Ser Tyr Asn Leu Ile Val Lys Leu Gly Pro Glu Asp Leu

- 83 -

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              225                  230                  235                  240


        Ala Asn Leu Thr Ser Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
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        Arg Cys Asp His Ala Pro Asn Pro Cys Ile Glu Cys Gly Gln Lys Ser
                        260                  265                  270


        Leu His Leu His Pro Glu Thr Phe His His Leu Ser His Leu Glu Gly
                        275                  280                  285


        Leu Val Leu Lys Asp Ser Ser Leu His Thr Leu Asn Ser Ser Trp Phe
                290                  295                  300


        Gln Gly Leu Val Asn Leu Ser Val Leu Asp Leu Ser Glu Asn Phe Leu
        305                  310                  315                  320


        Tyr Glu Ser Ile Asn His Thr Asn Ala Phe Gln Asn Leu Thr Arg Leu
                        325                  330                  335


        Arg Lys Leu Asn Leu Ser Phe Asn Tyr Arg Lys Lys Val Ser Phe Ala
                        340                  345                  350


        Arg Leu His Leu Ala Ser Ser Phe Lys Asn Leu Val Ser Leu Gln Glu
                        355                  360                  365


        Leu Asn Met Asn Gly Ile Phe Phe Arg Ser Leu Asn Lys Tyr Thr Leu
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        Arg Trp Leu Ala Asp Leu Pro Lys Leu His Thr Leu His Leu Gln Met
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        Asn Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Thr Phe Arg Ala
                        405                  410                  415


        Leu Arg Phe Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Pro Ser Thr
                        420                  425                  430


        Leu Ser Glu Ala Thr Pro Glu Glu Ala Asp Asp Ala Glu Gln Glu Glu
                        435                  440                  445


        Leu Leu Ser Ala Asp Pro His Pro Ala Pro Leu Ser Thr Pro Ala Ser
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Lys Asn Phe Met Asp Arg Cys Lys Asn Phe Lys Phe Thr Met Asp Leu
465   470   475   480

Ser Arg Asn Asn Leu Val Thr Ile Lys Pro Glu Met Phe Val Asn Leu
                  485   490   495

Ser Arg Leu Gln Cys Leu Ser Leu Ser His Asn Ser Ile Ala Gln Ala
              500   505   510

Val Asn Gly Ser Gln Phe Leu Pro Leu Thr Asn Leu Gln Val Leu Asp
          515   520   525

Leu Ser His Asn Lys Leu Asp Leu Tyr His Trp Lys Ser Phe Ser Glu
      530   535   540

Leu Pro Gln Leu Gln Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe
545   550   555   560

Ser Met Lys Gly Ile Gly His Asn Phe Ser Phe Val Ala His Leu Ser
                  565   570   575

Met Leu His Ser Leu Ser Leu Ala His Asn Asp Ile His Thr Arg Val
              580   585   590

Ser Ser His Leu Asn Ser Asn Ser Val Arg Phe Leu Asp Phe Ser Gly
      595   600   605

Asn Gly Met Gly Arg Met Trp Asp Glu Gly Gly Leu Tyr Leu His Phe
      610   615   620

Phe Gln Gly Leu Ser Gly Leu Leu Lys Leu Asp Leu Ser Gln Asn Asn
625   630   635   640

Leu His Ile Leu Arg Pro Gln Asn Leu Asp Asn Leu Pro Lys Ser Leu
              645   650   655

Lys Leu Leu Ser Leu Arg Asp Asn Tyr Leu Ser Phe Phe Asn Trp Thr
              660   665   670

Ser Leu Ser Phe Leu Pro Asn Leu Glu Val Leu Asp Leu Ala Gly Asn
      675   680   685

Gln Leu Lys Ala Leu Thr Asn Gly Thr Leu Pro Asn Gly Thr Leu Leu
      690   695   700

Gln Lys Leu Asp Val Ser Ser Asn Ser Ile Val Ser Val Val Pro Ala
705   710   715   720

Phe Phe Ala Leu Ala Val Glu Leu Lys Glu Val Asn Leu Ser His Asn
              725   730   735

Ile Leu Lys Thr Val Asp Arg Ser Trp Phe Gly Pro Ile Val Met Asn
              740   745   750

Leu Thr Val Leu Asp Val Arg Ser Asn Pro Leu His Cys Ala Cys Gly
          755   760   765

Ala Ala Phe Val Asp Leu Leu Leu Glu Val Gln Thr Lys Val Pro Gly
      770   775   780

Leu Ala Asn Gly Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg
785   790   795   800

Ser Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Val Leu Ser
              805   810   815

Trp Asp Cys Phe Gly Leu Ser Leu Leu Ala Val Ala Val Gly Met Val
          820   825   830

Val Pro Ile Leu His His Leu Cys Gly Trp Asp Val Trp Tyr Cys Phe
          835   840   845

His Leu Cys Leu Ala Trp Leu Pro Leu Leu Ala Arg Ser Arg Arg Ser
    850   855   860

Ala Gln Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Ala Gln
865   870   875   880

Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Val Arg Leu Glu
              885   890   895

Glu Arg Arg Gly Arg Arg Ala Leu Arg Leu Cys Leu Glu Asp Arg Asp
          900   905   910

Trp Leu Pro Gly Gln Thr Leu Phe Glu Asn Leu Trp Ala Ser Ile Tyr
    915   920   925

Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser
    930   935   940

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Gly Leu Leu Arg Thr Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu
945             950             955             960

Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Arg Pro Asp Ala His
                965             970             975

Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val
            980             985             990

Leu Phe Trp Pro Gln Gln Pro Asn Gly Gln Gly Gly Phe Trp Ala Gln
            995             1000            1005

Leu Ser Thr Ala Leu Thr Arg Asp Asn Arg His Phe Tyr Asn Gln
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Asn Phe Cys Arg Gly Pro Thr Ala Glu
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<213>   Mus musculus

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Met Val Leu Arg Arg Arg Thr Leu His Pro Leu Ser Leu Leu Val Gln
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Ala Ala Val Leu Ala Glu Thr Leu Ala Leu Gly Thr Leu Pro Ala Phe
            20              25              30

Leu Pro Cys Glu Leu Lys Pro His Gly Leu Val Asp Cys Asn Trp Leu
        35              40              45

Phe Leu Lys Ser Val Pro Arg Phe Ser Ala Ala Ala Ser Cys Ser Asn
    50              55              60

Ile Thr Arg Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asn
65              70              75              80

Ser Asp Phe Val His Leu Ser Asn Leu Arg Gln Leu Asn Leu Lys Trp
            85              90              95

Asn Cys Pro Pro Thr Gly Leu Ser Pro Leu His Phe Ser Cys His Met
        100             105             110
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Thr Ile Glu Pro Arg Thr Phe Leu Ala Met Arg Thr Leu Glu Glu Leu
        115   120   125

Asn Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Arg Leu Pro Ser Ser
    130   135   140

Leu Val Asn Leu Ser Leu Ser His Thr Asn Ile Leu Val Leu Asp Ala
145   150   155   160

Asn Ser Leu Ala Gly Leu Tyr Ser Leu Arg Val Leu Phe Met Asp Gly
                165   170   175

Asn Cys Tyr Tyr Lys Asn Pro Cys Thr Gly Ala Val Lys Val Thr Pro
            180   185   190

Gly Ala Leu Leu Gly Leu Ser Asn Leu Thr His Leu Ser Leu Lys Tyr
        195   200   205

Asn Asn Leu Thr Lys Val Pro Arg Gln Leu Pro Pro Ser Leu Glu Tyr
    210   215   220

Leu Leu Val Ser Tyr Asn Leu Ile Val Lys Leu Gly Pro Glu Asp Leu
225   230   235   240

Ala Asn Leu Thr Ser Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
                245   250   255

Arg Cys Asp His Ala Pro Asn Pro Cys Ile Glu Cys Gly Gln Lys Ser
            260   265   270

Leu His Leu His Pro Glu Thr Phe His His Leu Ser His Leu Glu Gly
        275   280   285

Leu Val Leu Lys Asp Ser Ser Leu His Thr Leu Asn Ser Ser Trp Phe
    290   295   300

Gln Gly Leu Val Asn Leu Ser Val Leu Asp Leu Ser Glu Asn Phe Leu
305   310   315   320

Tyr Glu Ser Ile Asn His Thr Asn Ala Phe Gln Asn Leu Thr Arg Leu
                325   330   335

Arg Lys Leu Asn Leu Ser Phe Asn Tyr Arg Lys Lys Val Ser Phe Ala

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                    340                      345                      350


     Arg Leu His Leu Ala Ser Ser Phe Lys Asn Leu Val Ser Leu Gln Glu
             355                  360                  365


     Leu Asn Met Asn Gly Ile Phe Phe Arg Ser Leu Asn Lys Tyr Thr Leu
         370                  375                  380


     Arg Trp Leu Ala Asp Leu Pro Lys Leu His Thr Leu His Leu Gln Met
     385                  390              .        395                  400


     Asn Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Thr Phe Arg Ala
                     405                  410                  415


     Leu Arg Phe Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Pro Ser Thr
                 420                  425                  430


     Leu Ser Glu Ala Thr Pro Glu Glu Ala Asp Asp Ala Glu Gln Glu Glu
             435                  440                  445


     Leu Leu Ser Ala Asp Pro His Pro Ala Pro Leu Ser Thr Pro Ala Ser
         450                  455                  460


     Lys Asn Phe Met Asp Arg Cys Lys Asn Phe Lys Phe Thr Met Asp Leu
     465                  470                  475                  480


     Ser Arg Asn Asn Leu Val Thr Ile Lys Pro Glu Met Phe Val Asn Leu
                 485                  490                  495


     Ser Arg Leu Gln Cys Leu Ser Leu Ser His Asn Ser Ile Ala Gln Ala
             500                  505                  510


     Val Asn Gly Ser Gln Phe Leu Pro Leu Thr Asn Leu Gln Val Leu Asp
         515                  520                  525


     Leu Ser His Asn Lys Leu Asp Leu Tyr His Trp Lys Ser Phe Ser Glu
         530                  535                  540


     Leu Pro Gln Leu Gln Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe
     545                  550                  555                  560


     Ser Met Lys Gly Ile Gly His Asn Phe Ser Phe Val Ala His Leu Ser
                 565                  570                  575
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Met Leu His Ser Leu Ser Leu Ala His Asn Asp Ile His Thr Arg Val
        580             585             590

Ser Ser His Leu Asn Ser Asn Ser Val Arg Phe Leu Asp Phe Ser Gly
        595             600             605

Asn Gly Met Gly Arg Met Trp Asp Glu Gly Gly Leu Tyr Leu His Phe
    610             615             620

Phe Gln Gly Leu Ser Gly Leu Leu Lys Leu Asp Leu Ser Gln Asn Asn
625             630             635             640

Leu His Ile Leu Arg Pro Gln Asn Leu Asp Asn Leu Pro Lys Ser Leu
            645             650             655

Lys Leu Leu Ser Leu Arg Asp Asn Tyr Leu Ser Phe Phe Asn Trp Thr
        660             665             670

Ser Leu Ser Phe Leu Pro Asn Leu Glu Val Leu Asp Leu Ala Gly Asn
        675             680             685

Gln Leu Lys Ala Leu Thr Asn Gly Thr Leu Pro Asn Gly Thr Leu Leu
    690             695             700

Gln Lys Leu Asp Val Ser Ser Asn Ser Ile Val Ser Val Val Pro Ala
705             710             715             720

Phe Phe Ala Leu Ala Val Glu Leu Lys Glu Val Asn Leu Ser His Asn
            725             730             735

Ile Leu Lys Thr Val Asp Arg Ser Trp Phe Gly Pro Ile Val Met Asn
        740             745             750

Leu Thr Val Leu Asp Val Arg Ser Asn Pro Leu His Cys Ala Cys Gly
    755             760             765

Ala Ala Phe Val Asp Leu Leu Leu Glu Val Gln Thr Lys Val Pro Gly
    770             775             780

Leu Ala Asn Gly Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg
785             790             795             800

Ser Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Val Leu Ser
            805             810             815
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Trp Asp Cys Phe Gly
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<213> Mus musculus

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-93-

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<212> PRT
<213> Homo sapiens

<400> 33

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Ala Ile Met Leu Ala Met Thr Leu Ala Leu Gly Thr Leu Pro Ala Phe
            20                  25                  30


Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu
        35                  40                  45


Phe Leu Lys Ser Val Pro His Phe Ser Met Ala Ala Pro Arg Gly Asn
    50                  55                  60


Val Thr Ser Leu Ser Leu Ser Ser Asn Arg Ile His His Leu His Asp
65                  70                  75                  80
```

.

```
Ser Asp Phe Ala His Leu Pro Ser Leu Arg His Leu Asn Leu Lys Trp
                85              90              95

Asn Cys Pro Pro Val Gly Leu Ser Pro Met His Phe Pro Cys His Met
            100             105             110

Thr Ile Glu Pro Ser Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu
        115             120             125

Asn Leu Ser Tyr Asn Asn Ile Met Thr Val Pro Ala Leu Pro Lys Ser
    130             135             140

Leu Ile Ser Leu Ser Leu Ser His Thr Asn Ile Leu Met Leu Asp Ser
145             150             155             160

Ala Ser Leu Ala Gly Leu His Ala Leu Arg Phe Leu Phe Met Asp Gly
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Asn Cys Tyr Tyr Lys Asn Pro Cys Arg Gln Ala Leu Glu Val Ala Pro
            180             185             190

Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr
        195             200             205

Asn Asn Leu Thr Val Val Pro Arg Asn Leu Pro Ser Ser Leu Glu Tyr
    210             215             220

Leu Leu Leu Ser Tyr Asn Arg Ile Val Lys Leu Ala Pro Glu Asp Leu
225             230             235             240

Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
            245             250             255

Arg Cys Asp His Ala Pro Asn Pro Cys Met Glu Cys Pro Arg His Phe
            260             265             270

Pro Gln Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly
        275             280             285

Leu Val Leu Lys Asp Ser Ser Leu Ser Trp Leu Asn Ala Ser Trp Phe
    290             295             300

Arg Gly Leu Gly Asn Leu Arg Val Leu Asp Leu Ser Glu Asn Phe Leu
```

```
305                     310                     315                     320
```

```
Tyr Lys Cys Ile Thr Lys Thr Lys Ala Phe Gln Gly Leu Thr Gln Leu
            325                 330                 335
```

```
Arg Lys Leu Asn Leu Ser Phe Asn Tyr Gln Lys Arg Val Ser Phe Ala
            340                 345                 350
```

```
His Leu Ser Leu Ala Pro Ser Phe Gly Ser Leu Val Ala Leu Lys Glu
            355                 360                 365
```

```
Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Asp Glu Thr Thr Leu
            370                 375                 380
```

```
Arg Pro Leu Ala Arg Leu Pro Met Leu Gln Thr Leu Arg Leu Gln Met
385                 390                 395                 400
```

```
Asn Phe Ile Asn Gln Ala Gln Leu Gly Ile Phe Arg Ala Phe Pro Gly
            405                 410                 415
```

```
Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ser Glu
            420                 425                 430
```

```
Leu Thr Ala Thr Met Gly Glu Ala Asp Gly Gly Glu Lys Val Trp Leu
            435                 440                 445
```

```
Gln Pro Gly Asp Leu Ala Pro Ala Pro Val Asp Thr Pro Ser Ser Glu
    450                 455                 460
```

```
Asp Phe Arg Pro Asn Cys Ser Thr Leu Asn Phe Thr Leu Asp Leu Ser
465                 470                 475                 480
```

```
Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Ala Gln Leu Ser
            485                 490                 495
```

```
His Leu Gln Cys Leu Arg Leu Ser His Asn Cys Ile Ser Gln Ala Val
            500                 505                 510
```

```
Asn Gly Ser Gln Phe Leu Pro Leu Thr Gly Leu Gln Val Leu Asp Leu
            515                 520                 525
```

```
Ser Arg Asn Lys Leu Asp Leu Tyr His Glu His Ser Phe Thr Glu Leu
    530                 535                 540
```

Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Gly
545   550   555   560

Met Gln Gly Val Gly His Asn Phe Ser Phe Val Ala His Leu Arg Thr
            565   570   575

Leu Arg His Leu Ser Leu Ala His Asn Asn Ile His Ser Gln Val Ser
        580   585   590

Gln Gln Leu Cys Ser Thr Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn
        595   600   605

Ala Leu Gly His Met Trp Ala Glu Gly Asp Leu Tyr Leu His Phe Phe
    610   615   620

Gln Gly Leu Ser Gly Leu Ile Trp Leu Asp Leu Ser Gln Asn Arg Leu
625   630   635   640

His Thr Leu Leu Pro Gln Thr Leu Arg Asn Leu Pro Lys Ser Leu Gln
            645   650   655

Val Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Lys Trp Trp Ser
        660   665   670

Leu His Phe Leu Pro Lys Leu Glu Val Leu Asp Leu Ala Gly Asn Arg
        675   680   685

Leu Lys Ala Leu Thr Asn Gly Ser Leu Pro Ala Gly Thr Arg Leu Arg
    690   695   700

Arg Leu Asp Val Ser Cys Asn Ser Ile Ser Phe Val Ala Pro Gly Phe
705   710   715   720

Phe Ser Lys Ala Lys Glu Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala
            725   730   735

Leu Lys Thr Val Asp His Ser Trp Phe Gly Pro Leu Ala Ser Ala Leu
            740   745   750

Gln Ile Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala
        755   760   765

Ala Phe Met Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu
    770   775   780

Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Leu Ser
785   790   795   800

Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu Ser Trp
            805   810   815

Asp Cys Phe Ala Leu Ser Leu Leu Ala Val Ala Leu Gly Leu Gly Val
            820   825   830

Pro Met Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His
            835   840   845

Leu Cys Leu Ala Trp Leu Pro Trp Arg Gly Arg Gln Ser Gly Arg Asp
    850   855   860

Glu Asp Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Thr Gln
865   870   875   880

Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Gly Gln Leu Glu
            885   890   895

Glu Cys Arg Gly Arg Trp Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp
        900   905   910

Trp Leu Pro Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr
    915   920   925

Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser
    930   935   940

Gly Leu Leu Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu
945   950   955   960

Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Ser Pro Asp Gly Arg
            965   970   975

Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val
        980   985   990

Leu Leu Trp Pro His Gln Pro Ser Gly Gln Arg Ser Phe Trp Ala Gln
    995   1000   1005

Leu Gly Met Ala Leu Thr Arg Asp Asn His His Phe Tyr Asn Arg
    1010   1015   1020

```
Asn Phe  Cys Gln Gly Pro Thr  Ala Glu
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```

```
<210>  34
<211>  820
<212>  PRT
<213>  Homo sapiens

<400>  34
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```
Met Gly Phe Cys Arg Ser Ala Leu His Pro Leu Ser Leu Leu Val Gln
1               5               10              15


Ala Ile Met Leu Ala Met Thr Leu Ala Leu Gly Thr Leu Pro Ala Phe
            20              25              30


Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu
        35              40              45


Phe Leu Lys Ser Val Pro His Phe Ser Met Ala Ala Pro Arg Gly Asn
    50              55              60


Val Thr Ser Leu Ser Leu Ser Ser Asn Arg Ile His His Leu His Asp
65              70              75              80


Ser Asp Phe Ala His Leu Pro Ser Leu Arg His Leu Asn Leu Lys Trp
            85              90              95


Asn Cys Pro Pro Val Gly Leu Ser Pro Met His Phe Pro Cys His Met
            100             105             110


Thr Ile Glu Pro Ser Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu
        115             120             125


Asn Leu Ser Tyr Asn Asn Ile Met Thr Val Pro Ala Leu Pro Lys Ser
    130             135             140


Leu Ile Ser Leu Ser Leu Ser His Thr Asn Ile Leu Met Leu Asp Ser
145             150             155             160


Ala Ser Leu Ala Gly Leu His Ala Leu Arg Phe Leu Phe Met Asp Gly
            165             170             175


Asn Cys Tyr Tyr Lys Asn Pro Cys Arg Gln Ala Leu Glu Val Ala Pro
            180             185             190
```

```
Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr
        195             200             205

Asn Asn Leu Thr Val Val Pro Arg Asn Leu Pro Ser Ser Leu Glu Tyr
    210             215             220

Leu Leu Leu Ser Tyr Asn Arg Ile Val Lys Leu Ala Pro Glu Asp Leu
225             230             235             240

Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
            245             250             255

Arg Cys Asp His Ala Pro Asn Pro Cys Met Glu Cys Pro Arg His Phe
            260             265             270

Pro Gln Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly
        275             280             285

Leu Val Leu Lys Asp Ser Ser Leu Ser Trp Leu Asn Ala Ser Trp Phe
    290             295             300

Arg Gly Leu Gly Asn Leu Arg Val Leu Asp Leu Ser Glu Asn Phe Leu
305             310             315             320

Tyr Lys Cys Ile Thr Lys Thr Lys Ala Phe Gln Gly Leu Thr Gln Leu
            325             330             335

Arg Lys Leu Asn Leu Ser Phe Asn Tyr Gln Lys Arg Val Ser Phe Ala
            340             345             350

His Leu Ser Leu Ala Pro Ser Phe Gly Ser Leu Val Ala Leu Lys Glu
        355             360             365

Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Asp Glu Thr Thr Leu
    370             375             380

Arg Pro Leu Ala Arg Leu Pro Met Leu Gln Thr Leu Arg Leu Gln Met
385             390             395             400

Asn Phe Ile Asn Gln Ala Gln Leu Gly Ile Phe Arg Ala Phe Pro Gly
            405             410             415

Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ser Glu
```

420   425   430

Leu Thr Ala Thr Met Gly Glu Ala Asp Gly Gly Glu Lys Val Trp Leu
        435   440   445

Gln Pro Gly Asp Leu Ala Pro Ala Pro Val Asp Thr Pro Ser Ser Glu
    450   455   460

Asp Phe Arg Pro Asn Cys Ser Thr Leu Asn Phe Thr Leu Asp Leu Ser
465   470   475   480

Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Ala Gln Leu Ser
            485   490   495

His Leu Gln Cys Leu Arg Leu Ser His Asn Cys Ile Ser Gln Ala Val
        500   505   510

Asn Gly Ser Gln Phe Leu Pro Leu Thr Gly Leu Gln Val Leu Asp Leu
    515   520   525

Ser Arg Asn Lys Leu Asp Leu Tyr His Glu His Ser Phe Thr Glu Leu
    530   535   540

Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Gly
545   550   555   560

Met Gln Gly Val Gly His Asn Phe Ser Phe Val Ala His Leu Arg Thr
            565   570   575

Leu Arg His Leu Ser Leu Ala His Asn Asn Ile His Ser Gln Val Ser
            580   585   590

Gln Gln Leu Cys Ser Thr Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn
        595   600   605

Ala Leu Gly His Met Trp Ala Glu Gly Asp Leu Tyr Leu His Phe Phe
    610   615   620

Gln Gly Leu Ser Gly Leu Ile Trp Leu Asp Leu Ser Gln Asn Arg Leu
625   630   635   640

His Thr Leu Leu Pro Gln Thr Leu Arg Asn Leu Pro Lys Ser Leu Gln
            645   650   655

```
Val Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Lys Trp Trp Ser
            660             665             670
```

```
Leu His Phe Leu Pro Lys Leu Glu Val Leu Asp Leu Ala Gly Asn Arg
            675             680             685
```

```
Leu Lys Ala Leu Thr Asn Gly Ser Leu Pro Ala Gly Thr Arg Leu Arg
            690             695             700
```

```
Arg Leu Asp Val Ser Cys Asn Ser Ile Ser Phe Val Ala Pro Gly Phe
705             710             715             720
```

```
Phe Ser Lys Ala Lys Glu Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala
            725             730 .           735
```

```
Leu Lys Thr Val Asp His Ser Trp Phe Gly Pro Leu Ala Ser Ala Leu
            740             745             750
```

```
Gln Ile Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala
            755             760             765
```

```
Ala Phe Met Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu
            770             775             780
```

```
Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Leu Ser
785             790             795             800
```

```
Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu Ser Trp
            805             810             815
```

```
Asp Cys Phe Ala
            820
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ctcctggtgc aggccatcat gctggccatg accctggccc tgggtacctt gcctgccttc     240

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ttcgtggtct tcgacaaaac gcagagcgca gtggcagact gggtgtacaa cgagcttcgg    2820

gggcagctgg aggagtgccg tgggcgctgg gcactccgcc tgtgcctgga ggaacgcgac    2880

tggctgcctg gcaaaaccct ctttgagaac ctgtgggcct cggtctatgg cagccgcaag    2940

acgctgtttg tgctggccca cacggaccgg gtcagtggtc tcttgcgcgc cagcttcctg    3000

ctggcccagc agcgcctgct ggaggaccgc aaggacgtcg tggtgctggt gatcctgagc    3060

cctgacggcc gccgctcccg ctacgtgcgg ctgcgccagc gcctctgccg ccagagtgtc    3120

ctcctctggc cccaccagcc cagtggtcag cgcagcttct gggcccagct gggcatggcc    3180

ctgaccaggg acaaccacca cttctataac cggaacttct gccagggacc cacggccgaa    3240

tagccgtgag ccggaatcct gcacggtgcc acctccacac tcacctcacc tctgcctgcc    3300

tggtctgacc ctcccctgct cgcctccctc accccacacc tgacacagag ca             3352
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<210>  36
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<212>  DNA
<213>  Homo sapiens

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gccatgaccc tggccctggg taccttgcct gccttcctac cctgtgagct ccagccccac    120

ggcctggtga actgcaactg gctgttcctg aagtctgtgc cccacttctc catggcagca    180

cccgtggca atgtcaccag cctttccttg tcctccaacc gcatccacca cctccatgat    240
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tctgactttg cccacctgcc cagcctgcgg catctcaacc tcaagtggaa ctgcccgccg    300

gttggcctca gccccatgca cttcccctgc cacatgacca tcgagcccag caccttcttg    360

gctgtgccca ccctggaaga gctaaacctg agctacaaca acatcatgac tgtgcctgcg    420

ctgcccaaat ccctcatatc cctgtccctc agccatacca acatcctgat gctagactct    480

gccagcctcg ccggcctgca tgccctgcgc ttcctattca tggacggcaa ctgttattac    540

aagaacccct gcaggcaggc actggaggtg gccccgggtg ccctccttgg cctgggcaac    600

ctcacccacc tgtcactcaa gtacaacaac ctcactgtgg tgccccgcaa cctgccttcc ·  660

agcctggagt atctgctgtt gtcctacaac cgcatcgtca aactggcgcc tgaggacctg    720

gccaatctga ccgccctgcg tgtgctcgat gtgggcggaa attgccgccg ctgcgaccac    780

gctcccaacc cctgcatgga gtgccctcgt cacttccccc agctacatcc cgataccttc    840

agccacctga gccgtcttga aggcctggtg ttgaaggaca gttctctctc ctggctgaat    900

gccagttggt tccgtgggct gggaaacctc cgagtgctgg acctgagtga gaacttcctc    960

tacaaatgca tcactaaaac caaggccttc cagggcctaa cacagctgcg caagcttaac   1020

ctgtccttca attaccaaaa gagggtgtcc tttgcccacc tgtctctggc cccttccttc   1080

gggagcctgg tcgccctgaa ggagctggac atgcacggca tcttcttccg ctcactcgat   1140

gagaccacgc tccggccact ggcccgcctg cccatgctcc agactctgcg tctgcagatg   1200

aacttcatca ccaggcccag ctcggcatc ttcagggcct tccctggcct gcgctacgtg    1260

gacctgtcgg acaaccgcat cagcggagct tcggagctga cagccaccat gggggaggca   1320

gatggagggg agaaggtctg gctgcagcct ggggaccttg ctccggcccc agtggacact   1380

cccagctctg aagacttcag gcccaactgc agcaccctca acttcacctt ggatctgtca   1440

cggaacaacc tggtgaccgt gcagccggag atgtttgccc agctctcgca cctgcagtgc   1500

ctgcgcctga ccacaactg catctcgcag gcagtcaatg ctcccagtt cctgccgctg     1560

accggtctgc aggtgctaga cctgtcccgc aataagctgg acctctacca cgagcactca   1620

ttcacggagc taccgcgact ggaggccctg acctcagct acaacagcca gccctttggc     1680

atgcagggcg tgggccacaa cttcagcttc gtggctcacc tgcgcacccl cgccacctc    1740

agcctggccc acaacaacat ccacagccaa gtgtcccagc agctctgcag tacgtcgctg   1800

cgggccctgg acttcagcgg caatgcactg ggccatatgt gggccgaggg agacctctat   1860

ctgcacttct tccaaggcct gagcggtttg atctggctgg acttgtccca gaaccgcctg   1920

cacaccctcc tgccccaaac cctgcgcaac ctccccaaga gcctacaggt gctgcgtctc   1980

cgtgacaatt acctggcctt ctttaagtgg tggagcctcc acttcctgcc caaactggaa   2040
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gtcctcgacc tggcaggaaa ccggctgaag gccctgacca atggcagcct gcctgctggc   2100

acccggctcc ggaggctgga tgtcagctgc aacagcatca gcttcgtggc ccccggcttc   2160

ttttccaagg ccaaggagct gcgagagctc aaccttagcg ccaacgccct caagacagtg   2220

gaccactcct ggtttgggcc cctggcgagt gccctgcaaa tactagatgt aagcgccaac   2280

cctctgcact gcgcctgtgg ggcggccttt atggacttcc tgctggaggt gcaggctgcc   2340

gtgcccggtc tgcccagccg ggtgaagtgt ggcagtccgg gccagctcca gggcctcagc   2400

atctttgcac aggacctgcg cctctgcctg gatgaggccc tctcctggga ctgtttcgcc   2460
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<210>   37
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<212>   DNA
<213>   Artificial sequence

<220>
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<400>   37
accttgcctg ccttcctacc ctgtga                                         26


<210>   38
<211>   21
<212>   DNA
<213>   Artificial sequence

<220>
<223>   Synthetic oligonucleotide

<400>   38
gtccgtgtgg gccagcacaa a                                              21


<210>   39
<211>   20
<212>   DNA
<213>   Artificial sequence

<220>
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<400>   39
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<210>   40
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<220>
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<210> 41
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<220>
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<400> 41
tccatcacgt ttttgatgtt                                                       20


<210> 42
<211> 20
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<220>
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<400> 42
tccattacgt ttttgatgtt                                                       20


<210> 43
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<220>
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<400> 43
tccatggcgt ttttgatgtt                                                       20


<210> 44
<211> 20
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<220>
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<400> 44
tccatgccgt ttttgatgtt                                                       20


<210> 45
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<212> DNA
<213> Artificial sequence

<220>
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<223> Synthetic oligonucleotide

<400> 45
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<210> 46
<211> 20
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<220>
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<400> 46
tccatgatgt ttttgatgtt   20

<210> 47
<211> 20
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<220>
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<400> 47
tccatgaagt ttttgatgtt   20

<210> 48
<211> 20
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<220>
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<400> 48
tccatgaggt ttttgatgtt   20

<210> 49
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<400> 49
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<210> 50
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<400> 50
tccatgacct ttttgatgtt   20

<210> 51
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<210> 52
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<400> 52
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<210> 53
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<400> 53
tccatgacga ttttgatgtt   20

<210> 54
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<400> 54
tccatgacgg ttttgatgtt   20

<210> 55
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tccatgacgt ctttgatgtt   20

<210> 56
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<210> 57
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<210> 58
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<220>
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<400> 58
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<210> 59
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<400> 59
tgctgctttt gtgcttttgt gctt   24

<210> 60
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<400> 60
tccatgacgt tcctgatgct   20

<210> 61
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<400> 61
tccatgagct tcctgatgct   20

<210> 62
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<213> Artificial sequence

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<223> Any amino acid

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<223> Any amino acid

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Gly Asn Cys Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Cys
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<210> 63
<211> 16
<212> PRT
<213> Homo sapiens

<400> 63

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1               5                   10                  15


<210>  64
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<212>  PRT
<213>  Mus musculus


<400>  64

Gly Asn Cys Arg Arg Cys Asp His Ala Pro Asn Pro Cys Met Ile Cys
1               5                   10                  15


<210>  65
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<220>
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<400>  65

Arg Xaa Xaa Xaa Xaa Xaa Xaa Xaa Arg Xaa Asp Xaa Tyr Xaa Xaa Xaa
1               5                   10                  15
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Xaa Xaa Xaa Xaa Xaa Xaa Arg Ser Xaa Xaa Xaa Xaa Xaa Xaa Tyr
            20                  25                  30


<210>  66
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<222>  (25)..(30)
<223>  Any amino acid


<400>  66

Gln Xaa Xaa Xaa Xaa Xaa Xaa Xaa Lys Xaa Asp Xaa Tyr Xaa Xaa Xaa
1               5                   10                  15


Xaa Xaa Xaa Xaa Xaa Xaa Arg Leu Xaa Xaa Xaa Xaa Xaa Xaa Tyr
            20                  25                  30


<210>  67
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<400>  67

Gln Xaa Xaa Xaa Xaa Xaa Xaa Xaa Lys Xaa Asp Xaa Tyr Xaa Xaa Xaa
1               5                   10                  15


Xaa Xaa Xaa Xaa Xaa Xaa Gln Leu Xaa Xaa Xaa Xaa Xaa Tyr
            20                  25                  30


<210>  68
<211>  31
<212>  PRT
<213>  Homo sapiens

<400>  68

Gln Val Leu Asp Leu Ser Arg Asn Lys Leu Asp Leu Tyr His Glu His
1               5                   10                  15


Ser Phe Thr Glu Leu Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr
            20                  25                  30


<210>  69
<211>  31
<212>  PRT
<213>  Mus musculus

<400>  69

Gln Val Leu Asp Leu Ser His Asn Lys Leu Asp Leu Tyr His Trp Lys
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1                    5                    10                    15
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Ser Phe Ser Glu Leu Pro Gln Leu Gln Ala Leu Asp Leu Ser Tyr
              20   25   30

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<212>  DNA
<213>  Artificial sequence

<220>
<223>  Synthetic oligonucleotide

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